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A logot Mátyássy László tervezte. Egy nyolcszögből (octogon) és egy mandula alakú résből az ún. mandorla-ból áll. Az octogon, vagyis a nyolcas szám az átváltozást (megújulást, újra születést), a mandorla pedig a szeméremtestet jelöli. A logo a női nemiszervek átváltozásának (pl. ismeretlen kimenetelű rákos megbetegedés) jelképe.

The embleme, designed by László Mátyássy, symbolizes a transition related to the female genital system, such as gynecologic cancer of unknown outcome. It is composed of an octogon and a mandorla. Octogon means eight which is the number of transition (renewal, rebirth), the mandorla is an almond-shape aureole representing the vulva.

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This number contains the proceedings published as review articles of the following Europen School of Oncology course

The place of radioton therapy in the management of gynecologic malignancies and breast cancer

Under the auspices of the Hungarian Academy of Sciences
September 26th-27th, 1996, Budapest, Hungary

European School of Oncology

CHAIRPERSONS: PÉTER BŐSZE, M.D. – SÁNDOR ECKHARDT, M.D. – ROBERTO ORECCHIA, M.D. – SERGIO PECORELLI, M.D.

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The objective of this course is to provide practicing gynecologic oncologists with new insight and information concerning radiation therapy of patients with malignant tumors of the female genital tract and breasts. The program focuses on both indications and techniques of irradiation. An in-depth discussion of some of the controversies relevant to radiation therapy of the primary tumor and lymph nodes are provided. This issue of the Hungarian Journal of Gynecologic Oncology is devoted to the proceedings of this course published as review articles to fullfil its major goals to provide a state of the art and to give guidelines on radiation therapy of women with gynecologic malignancies.

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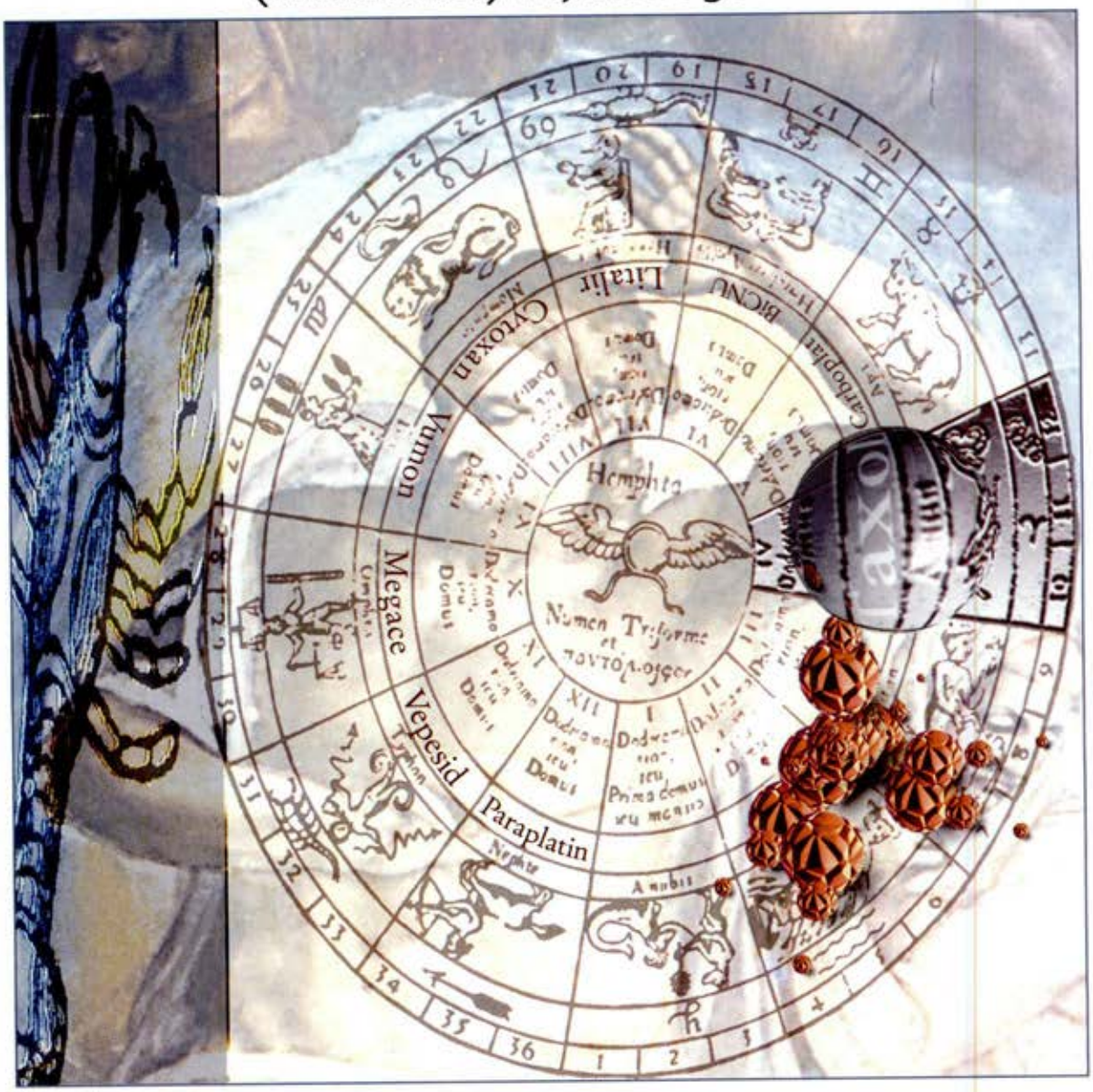

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The value of ultrasound in preirradiation work-up

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INTRODUCTION The pathways of spread of cervical and endometrial carcinoma form the basis for the system of staging. The purpose of any staging system is to provide a standardized means of assessing severity and extent of disease, which in turn should help guide patient management. Staging should also provide a means of assessing prognosis. A standardized system allows more scientific comparison of different methods of treatment as treatment strategies evolve. In the absence of a surgical specimen and surgical exploration, the extent of tumor spread (stage) must be established based on findings on physical examination as well as simple and sophisticated radiologic tests. In order to standardize staging between different institutions and take differences of availability of equipment and tests into account, only limited test are "allowed" as part of the staging process (inspection of cervix and vagina, colposcopy, biopsy, endocervical curettage, conization, hysteroscopy, chest radiography, skeletal radiography, intravenous urography, barium enema, cystoscopy, sigmoidoscopy).

When discussing diagnostic tests, it is common to concentrate on the sensitivity and specificity of the test. It is therefore important to make clear the definition of these terms. When results of imaging tests are correlated with histopathologic findings, the results of these tests can be classified into one of four categories: *True positive, (TP)* (the test is positive and the pathologic evaluation is positive), *False positive, (FP)* (the test is positive and the pathologic evaluation is negative), *True negative, (TN)* (the test is negative and the pathologic evaluation is negative), *False negative, (FN)* (the test is negative and the pathologic evaluation is positive). The *sensitivity (SN)* of a test is the probability that the test will indicate the *presence of an abnormality* given that the abnormality is present. Therefore $SN=TP/(TP+FN)$. The *specificity (SP)* of a test will indicate the *absence of an abnormality* given that the abnormality is not present. Thus, $SP=TN/(TN+FP)$. Therefore the sensitivity and specificity of a test predict the outcome of the test based upon whether an abnormality is present or absent.

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However, when therapeutic decisions are made based on the results of a given test, it is more appropriate to discuss the predictive values of the test. The *positive predictive value (PPV)* of a test is the probability that an abnormality will be present given that the test is positive, that is, $PPV=TP/(TP+FP)$. The *negative predictive value (NPV)* of a test is the probability that an abnormality will be absent given that the test is negative, that is, $NPV=TN/(TN+FN)$. Therefore the PPV and NPV predict the presence or absence of disease based on test results. When applied to the staging of cancer, an ideal imaging test should therefore have the following characteristics: 1) near 100% NPV, and/or near 100% PPV for those findings that result in a significant change in treatment modality, 2) be readily available to the general population, and *3)* be reproducible and not highly operator dependent. *Accuracy=(TP+TN)/Total number of examinations.*

CERVICAL CARCINOMA Most patients with microinvasive cervical carcinoma can be treated with simple hysterectomy. Patients with early invasive cervical carcinoma have several treatment options (radiation therapy alone, radical surgery alone, or combined radiotherapy and surgery). Patients with FIGO stages IIb, III and IV are usually treated with radiation therapy.

DISTINCTION BETWEEN THE SUBTYPES OF CIN AND BETWEEN CIN AND MICROINVASION can only be made based on histopathologic findings. A normal ultrasound (US) and magnetic resonance imaging (MRI) appearance requires further investigation to exclude early invasive disease (1).

PARAMETRIAL INVASION The next important step in the staging of cervical carcinoma is the determination of the presence or absence of parametrial invasion. This distinction is crucial because patients with parametrial invasion are usually candidates for radiation therapy. Transrectal ultrasound technique can be used to demonstrate the cervix and parametria using a standard radial rotating transducer to produce axially oriented images. *Yuhara and his co-workers* (2) performed this technique in 180 cases of stage IB, IIA or IIB uterine cervical cancer. Increases in the parametrial length, width, their product and internal echo intensity as well as shift of the cervix to the side of more severe induration were demonstrated. A parametrial echo wider than 1.0 cm indicates parametrial indu-

Table 1. Parametrial infiltration by cervical carcinoma assessed by transrectal radial ultrasonographic scanning, according to different characteristics. Total: 180 patients (2)

	SN(%)	SP(%)	PPV(%)	NPV(%)
Mass formation	15	100	100	90
Parametrial irregularity	52	41	9.6	88
Internal echo disorder	50	47	1	88
Overall	39	63	37	87

Overall accuracy: 60%

SN=Sensitivity SP=Specificity PPV=Positive predictive value NPV=Negative predictive value

ration and suspicion of parametrial infiltration. Mass formation on sonography had a 15% SN, 100% SP, 100% PPV, 90% NPV, irregularity of parametrial margin had a 52% SN, 41% SP, 9.6% PPV, 88% NPV, disorder of internal echoes had a 50% SN, 47% SP, 1% PPV, 88% NPV. Overall sensitivity was 39%, specificity 63%, PPV 37%, NPV 87%, accuracy 60% *(Table 1)*. A prospective study by *Cobby et al.* (3) compared the findings of endosonography, CT and MRI in 37 patients with invasive carcinoma of the cervix. Pathological correlation was available for 20 patients (13 stage IB, 2 IIB, 4 IIIB, 1 IV). Unlike *Yuhara et al.* (2), they found supporting previous findings (4) that on endosonography the parametrial morphological appearance is superior to parametrial measurement in determining parametrial involvement. It can be difficult to separate the parametrium from the edge of the cervix and variations in parametrial width with parity and inflammation have also been described.

With combined radial and sagittal scanning tumor volume can be calculated which is important for treatment planning and prognosis (5).

On MRI examination if the low signal intensity ring of cervical stroma is preserved, then the tumor is confined to the cervix (6), but in the presence of full thickness stroma invasion it is not possible to exclude microscopic parametrial spread. Parametrial involvement is shown by irregularity of the cervical margins associated with full thickness disruption of the low signal intensity stroma and abnormal signal or mass in the parametrial region. MRI in the sagittal plane is useful for showing vaginal wall involvement, extension into the body of the uterus or forwards to the bladder wall (7). In those 20 patients having pathological staging available, examination under anesthesia (EUA) agreed with the pathological staging in 17, understaging 3 patients. Endosonography agreed with staging in 19, understaged 1 (stage IV), CT in 16, understaged 2, overstaged 2, MRI in 18, understaged 1, overstaged 1 patients. Overall accuracy for EUA was 85%, for endosonography 95%, for CT 80%, for MRI 90%, respectively.

VAGINAL, PELVIC SIDEWALL, BLADDER, AND RECTAL INVOLVEMENT The ability of MRI to determine accurately vaginal, pelvic sidewall, bladder, and rectal involvement in patients with cervical carcinoma has been evaluated in a limited number of studies. In one study (7) the bladder wall involvement was well demonstrated by MRI in one patient with stage IV disease. From our experience, it appears that the NPV of endosonography is high in the context.

LYMPH NODES MRI signal characteristics of lymph nodes have not been shown to be useful in determining the presence or absence of metastatic disease. MRI, CT and sonographic imaging relies on detection of enlargement of lymph nodes to predict involvement by metastatic disease. The presence of metastatic disease in superficial enlarged nodes might be detected with flow measurements.

ENDOMETRIAL CARCINOMA Imaging modalities have their greatest utility in evaluating patients with histopathologically proven endometrial carcinoma. The greatest part of endometrial carcinoma patients will have stage I disease at the time of diagnosis. The two major prognostic factors affecting therapeutic decision and survival are tumor grade and depth of myometrial invasion by the tumor. In the pretreatment workup, tumor grade can be evaluated by pathologic examination of the D and C specimen of the uterine cavity.

DEPTH OF MYOMETRIAL INVASION Depth of invasion can however be estimated preoperatively only by performing imaging studies. In patients unfit for surgery, knowledge of degree of myometrial involvement is essential for planning radiation therapy (8).

MRI examinations appear to have an accuracy of 75% and 95% in distinguishing superficial from deep myometrial invasion (9-13).

These studies show that an intact junctional zone between endometrium and myometrium has an almost 100% NPV in excluding myometrial invasion, and that segmental disruption of the junctional zone has an almost 100% PPV in detecting myometrial invasion. Most patients with endometrial carcinoma, however, are postmenopausal and uterine zonal structure is usually diminished. Certain tumors have a polypoid appearance (14), with considerable size, distorting the zonal anatomy of the myometrium, giving way not to assess correctly the depth of invasion. The only solution is provided by assessing appearance of endometrial/myometrial interface: in case of irregularity invasion is highly probable, when this interface appears linear, no invasion is suspected to be present. NPV of near 100% is found assessing cervical involvement by tumor in MRI studies, however positive MRI data are limited regarding the much smaller number of patients with cervical involvement. Evaluating stage III and IV disease patients, MRI seems to have a high NPV for determining advanced disease, PPV is more difficult to evaluate due to the small number of stage III and IV endometrial carcinoma patients.

Transvaginal sonography proved to be superior to the transabdominal scan in the evaluation of the local extension of endometrial carcinoma regarding myometrial invasion (15-19). *Obata et al.* (20) used comparable results using radial scanning of the uterine cavity, measuring both degree of myometrial invasion and tumor volume. In the study of *Fleischer et al.* (21) subendometrial halo disruption was used as a sign for myometrial invasion. However, similarly to MRI, inaccuracy is due to distortion of endometrial cavity in patients with large polypoid tumors and fibroids. The number of patients participating in the studies is rather small to draw significant conclusions regarding sensitivity and specificity. Number of participating patients, accuracy of the test, ultrasound imaging modalities are summarized in *Table 2*. In our series (23) of 69 patients with endometrial carcinoma an overall 98 % accuracy was achieved assessing depth of myometrial tumor invasion.

Table 2. Accuracy in the assessment of depth of myometrial infiltration in endometrial carcinoma according to authors and techniques

Authors		Techn.	Accuracy (%) TP+TN/Total	year
Obata, et al.	(20)	IRS	26/32 (81)	1985
Lehtovirta, et al.	(22)	TAS	19/24 (79.3)	1987
Fleischer, et al.	(21)	TAS	16/20 (80)	1987
Cacciatore, et al.	(15)	TVS	20/23 (87)	1989
Sahakian, et al.	(16)	TVS	16/18 (88.8)	1991
Artner, et al.	(23)	TVS	68/69 (98)	1994

IRS=Intrauterine Radial Scanning TAS=Transabdominal Sonography

TVS=Transvaginal Sonography TP=True positive TN=True negative
Total=Total number of patients examined

The inner half of myometrium was involved in 28 patients, the outer half in 31, and there was no myometrial invasion in 10 cases. The corresponding values for ultrasound were 29, 31 and 9 respectively. There was only 1 false positive and no false negative results. The concordance between the sonographic and histological findings is significant ($p<0.001$). In the only woman with a false positive result sonography depicted irregular interface between the endometrium and myometrium *(Table 3)*.

DEPTH OF CERVICAL INVASION Data regarding assessment of depth of cervical invasion by endometrial carcinoma are too small, due to the fact that most patients having histological proof of this disease appear to have stage I disease after laparotomy specimen evaluation. Those false negatives on sonographic evaluation appeared to have microscopic invasion of cervix on histological examination (15). In our series (23) of 63 cervical sonography studies sonographically no sign of tumor invasion was observed. However on histological review, 2 of these were found to have only microscopices cervical invasion by the endometrial tumor, and in one histology demonstrated disease extending low to the inner cervical os, and was considered involvement of the cervix. There was no false positive finding in this study *(Table 4)*. Sensitivity, specificity, negative predictive value, positive predictive value of determining cervical infiltration are demonstrated in *Table 5*.

Table 3. Assessment of depth of myometrial involvement in endometrial carcinoma by transvaginal sonography, compared to pathological results using 3 classes of depths of myometrial invasion (23)

Pathology	Transvaginal sonography			
	No myometrial invasion	Inner half	Outer half	Total
No myometrial invasion	9	1	0	10
Inner half	0	28	0	28
Outer half	0	0	31	31
Total	9	29	31	69

Accuracy: 68/69= 98%

Table 4. Assessment of presence of cervical infiltration (23)

	Transvaginal sonography		
Pathology	infiltration	no infiltration	Total
infiltration	6	3	9
no infiltration	0	60	60
Total	6	63	69

False negatives:
- 2 cases showed microscopical involvement
- 1 case showed tumor extended low to the inner cervical os

Table 5. Assessment of cervical involvement by endometrial carcinoma (23)

Specificity	100%
Sensitivity	66%
Negative predictive value	95%
Positive predictive value	100%
Accuracy	95%

CONCLUSIONS

- Intracavitary ultrasonography shows a high accuracy rate in determining parametrial involvement in cervical carcinoma.
- Intracavitary sonoghaphy is able to assess myometrial and cervical invasion rate by endometrial carcinoma at high

concordance with pathological results.

- Ultrasonographic examination shows a high NPV when assessing bladder and rectal wall infiltration by cervical cancer, therefore, a negative study means a great probability that the organ examined is free of tumor.
- However, size and shape of lymph nodes on ultrasonographic evaluation do not carry a specific sign for the presence of tumor tissue, color Doppler studies show a promising way of detecting neoplastic growth via detecting neovascularisation in enlarged lymph nodes.

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Brachytherapy for pediatric malignancies

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INTRODUCTION Knowing the advantages of brachytherapy based on the experience acquired in adult patients, the question is, is it feasible to use brachytherapy in childhood neoplasms?

The objective of this lecture is to try to demonstrate the relevance of this kind of irradiation procedure concentrating on
– the different technical aspects of interstitial and endocavitary brachytherapy,
– the comparison between low dose-rate (LDR) and high dose-rate (HDR) brachytherapy,
– the results according to the main tumor sites in which brachytherapy can be used taking into account the literature review and more particularly the experience of the Institut Gustave-Roussy.

BRACHYTHERAPY: DEFINITIONS, RULES By delivering a high dose of radiation to a well defined volume with a low dose to the surrounding tissues, brachytherapy allows an elevated local tumor control with an acceptable rate of complications. According to the different ways to implant patients, two kinds of brachytherapy are generally defined:
– interstitial brachytherapy in which radioactive sources are implanted inside the tumor tissues to be irradiated
– endocavitary brachytherapy using a natural cavity of the human body in which radioactive sources are introduced in contact with the tumor tissues to be irradiated.

For brachytherapy it is necessary to have knowledge of the tumor volume to be treated and the tolerance of the surrounding normal tissues. Rules of an implant system must be respected in order to achieve a homogenous dose distribution. It is also important that the brachytherapy implant should be well tolerated by the child. Hospitalisation will be necessary when using LDR brachytherapy. Radiation exposure to medical staff and visitors will need to be minimised.

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To achieve these different objectives, modern brachytherapy is based on the use of afterloading systems (plastic tubes, guide gutters, hypodermic and guide needles, silk threads, catheters, templates, endocavitary applicators) miniaturized sources (iodine, cesium, iridium), remote afterloading machines, computerized dosimetry.

All these systems are used daily in adult patients and of course can be adapted to children. Before deciding on brachytherapy, it is quite necessary to know the volume to be implanted and to determine if it is possible to implant this volume, respecting the rules of a system. In case of negative response, the physician must be reasonalbe enough to accept that brachytherapy is not an option.

CLINICAL DATA Paediatric brachytherapy is rarely practised, but in selected cases, taking into account the experience acquired in adult patients, has it a definite benefit? Can brachytherapy combined with other modalities allow surgery to be more conservative with better functional results? Can we, with brachytherapy, decrease the complication rate as we observe with external beam irradiation?

To try to answer these different questions, it appears from the published literature, that paediatric brachytherapy is practised relatively rarely. As *Plowman* (1) said: "This is partly because of the extensive nature of many paediatric tumours... availability of electron beam facilities... relative lack of paediatric brachytherapy experience by radiotherapists". Along with these factors, it would be necessary to add that the high chemosensitivity of many neoplasms in children and the very important progress made with new drugs, and also the fact that many paediatricians are concerned with radiation therapy complications and sequellae. All these factors explain the few cases of children, presenting with cancer treated with brachytherapy.

So to try determining different tumor sites which can benefit from brachytherapy, we will describe firstly our own experience to be compared to the literature data in the discussion.

THE INSTITUT GUSTAVE-ROUSSY EXPERIENCE

POPULATION From 1972 to 1990, 127 children were treated with brachytherapy in the Institut Gustave-Roussy. During the same

period, 13 cases of retinoblastoma received intra-operative brachytherapy but they are excluded from this retrospective study. The main tumor sites are pelvis (57%), head and neck (33%), other soft tissues sarcomas (10%) and the pathological distribution shows rhabdomyosarcoma (53%), clear cell (27%), others (20%). The majority of the tumors treated were non-metastatic to distant organs.

TREATMENT PROTOCOL The primary aim of any treatment is to cure and, particularly in young patients, to try to preserve function and avoid radiation sequellae. So for pelvic cancers, radical surgery like prostatectomy, cystectomy, hysterectomy or pelvic exenteration have sometimes to be performed as first line treatment; however, our challenge was to find a way of preserving the sexual life, the hormonal function and perhaps even, the potential fertility of the cured child.

For all histological types except clear cell adenocarcinoma, the treatment was a combination of chemotherapy, surgery, brachytherapy and, in some cases, external radiotherapy. For clear cell adenocarcinoma, the treatment combined conservative surgery and brachytherapy with external radiotherapy in some cases. For all tumors the type of surgery varied depending on the tumor's location: tumor resection, lymphadenectomy, ovarian transposition or intraoperative brachytherapy. Furthermore surgery played a major role in case of local failure.

Chemotherapy was used, as usual for chemosensitive tumors, to reduce tumor volume in localized cases to make them accessible to brachytherapy, and to prevent distant metastases. Except in clear cell adenocarcinoma which is not a chemosensitive tumor, chemotherapy was essential in this combined treatment. It was mainly used at the beginning with an average of six courses. Different combinations of drugs were prescribed according to the histological types. In malignant mesenchymal tumors, prior to 1984, VAC (Vincristine, Actinomycin D and Cyclophosphamide) and VAD (Vincristine and Adriamycin) protocols were used. Then Ifosfamide replaced Cyclophosphamide (IVA protocol). In germ cell tumors (including Yolk sac), the MAC regimen (Methotrexate, Actinomycin D, Cyclophosphamide) was replaced at the same period by new active combinations with Cisplatinum, Vinblastine and Bleomycin. For patients with a high metastatic risk this chemotherapy was continued after the brachytherapy for a mean time of one year.

External beam irradiation was not routinely prescribed, the radiotherapy modalities were brachytherapy in 90% of the cases and combined brachytherapy-external beam irradiation in 10% of the cases. The indications for external radiotherapy were essentially bulky and extended disease and/or nodal involvement.

BRACHYTHERAPY

Generalities In 74% of cases, LDR brachytherapy was, combined with other therapeutic modalities, the first line treatment; while in 26% of cases, the brachytherapy was prescribed for recurrence as a salvage treatment.

For brachytherapy, the *adult techniques-adapted for children* were used. The afterloading systems were essentially plastic tubes with sometimes guide gutters, silk wires and/or hypodermic needles for interstitial brachytherapy; for endocavitary brachytherapy, moulded personalized applicators were used in all cases. Iridium 192 sources were employed in the vast majority of the cases, Cesium 137 was reserved for gynecological applications in which the size of the mould allowed the use of these radio-active sources with source-projectors. The *dose* given by brachytherapy was between 45 and 65 Gy if brachytherapy was used only. If a combined treatment was made with external beam, a boost of 15 to 25 Gy was used. All brachytherapy was low dose rate (0.4-0.6 Gy/h) and the total dose was delivered in 1 to 3 courses for gynecological tumors and in 1 course for the other tumor sites. The *computerized dosimetry* was calculated according to the Paris System for interstitial brachytherapy and according to the ICRU recommendations for endocavitary brachytherapy. For every patient a very precise dose-distribution was obtained in term of the dose delivered to the tumor, to the surrounding critical organs (bladder, rectum, ovaries, spinal cord, lung...), to the nodes and to various selected and relevant points. For all patients, optimized three dimensional dosimetry was made.

Brachytherapy procedure examples To illustrate the practical aspects of the brachytherapy we have chosen five of the most common indications: a rhabdomyosarcoma of the naso-labial sulcus, a soft tissue sarcoma of the arm, a vaginal rhabdomyosarcoma, a bladder-prostate sarcoma and a cervico-vaginal clear cell adenocarcinoma.

RHABDOMYOSARCOMA OF THE NASO-LABIAL SULCUS The current and primary treatment protocol of a rhabdomyosarcoma is chemotherapy. There is no need of an adjuvant treatment if regression is complete. Conservative surgery, brachytherapy or intraoperative brachytherapy are indicated when a complete response is not obtained.

The brachytherapy is mostly done by three plastic tubes afterloaded with Iridium 192. The median tube passes through the bottom of the naso-labial sulcus; it is surrounded by two lateral tubes. The distance between tubes is about 10 mm and the length of the iridium wire varies from 15 to 30 mm depending upon the tumor size and child's anatomy. The delivered dose is 65 Gy or only 55 to 60 Gy in case of intraoperative brachytherapy when the surgical resection is complete. In this example, as in other interstitial brachytherapy implants we use a low dose rate brachytherapy delivering by a continuous irradiation from 800 to 1200 cGy a day.

SARCOMA OF THE ARM In this case intra-operative brachytherapy is systematically performed with a conservative surgical approach. After the frozen section, the plastic tubes are implanted and according to the definitive histological exam the loading

and the dose to deliver are decided: 1. If the resection is histologically complete the indication for brachytherapy can be discussed according to the clinical, surgical and pathological data. If the brachytherapy indication is sustained the dose is 50 Gy. 2. If the macroscopic resection is complete but the microscopic resection is incomplete the dose is 60 Gy. 3. In case of bulky residual disease brachytherapy can be indicated but as an anticipated boost, followed by an external beam irradiation in a larger volume. The dose of brachytherapy must be about 25 to 30 Gy, as a boost; later the external beam irradiation will deliver 45 to 50 Gy.

BLADDER-PROSTATE RHABDOMYOSARCOMA Brachytherapy is indicated for small residual disease persisting after chemotherapy. The CT scan and MRI are necessary to confirm the indication for brachytherapy which is applied only intra-operatively. The first step of the conservative surgery is exploration of abdominal and pelvic cavities, lymphadenectomy and if possible, resection of the residual disease. The residual disease is mostly situated between bladder and prostate which is difficult to access by the brachytherapist. 2 to 3 plastic tubes are implanted through abdominal or perineal way according to the tumoral site. The residual disease should be clipped to enable the adapted afterloading.

In spite of the residual disease, normal tissue tolerance and histological data the dose delivered varies from 50 to 65 Gy. The calculation of the dose distribution is based on the Paris System rules, using a computerized system. Each time it's necessary we do a CT scan when the plastic tubes are implanted and before loading to check their position according to residual disease, critical organs and adapt dose distribution. Same procedure can be used in all brachytherapy implantations in adults as in children.

VAGINAL RHABDOMYOSARCOMA After chemotherapy in case of incomplete response the tumor volume is modified, the residual disease is often less exophytic. Only the vaginal mould, done under general anesthesia, enables a good visualisation of the tumor's topography. Fabrication of the mould, determination of the plastic tubes inserted on the applicator which will contain the iridium wires who's active length is chosen depending on the site to be irradiated and the critical organs.

After silver seeds are inserted to determine the tumor spread, the vaginal mould is introduced under general anesthesia. The bladder and the rectum are visualised with radio-opaque catheters. Radiological controls are done and dosimetry performed by computer. The total dose given to the tumor is 60 Gy. The rules used to decide the overall treatment time are identical to those used for the cervical carcinoma in adult patients with a special concern about the critical organs. If the dose received by these organs is too high the brachytherapy is done in multiple sessions to take into account the tumoral shrinking and adapting the irradiated volume to reduce the dose to surrounding normal tissues.

CLEAR CELL ADENOCARCINOMA (CCA) Unlike the other pediatric tumors clear cell adenocarcinoma is resistant to chemotherapy. The different steps of the treatment are:

- surgery with ovarian transposition and pelvic lymphadenectomy done by classic laparotomy or, more recently, with laparoscopy;
- in case of positive nodes or extended disease external beam irradiation prior to brachytherapy;
- in other cases postoperative brachytherapy.

The moulded applicator is the first step of the brachytherapy procedure. The principles of this brachytherapy is strictly the same as the principles of the brachytherapy of the carcinoma of uterine cervix in adult females. One should stress the difficulties due to the anatomy of these adolescents who mostly didn't have a sexual experience, nulliparity with small vaginas which are frequently malformed. Because of these aspects, the moulded applicator, and the radioactive sources must be perfectly adapted case by case as well as the dose distribution.

RESULTS

SOFT TISSUE SARCOMA Soft tissue sarcomas are divided according to the main sites:

- for trunk and limbs (13 patients) brachytherapy was used in 10 out of 13 patients as a salvage treatment. The 5-year disease-free survival (DFS) was 46%, the local control rate was 61%, and a 23% grades 2 and 3 complication rate was observed;
- for head and neck thirty nine patients received combined treatment including brachytherapy done 25 times as a first line treatment and 14 times as salvage treatment. The 5-year results, according to the two different approaches, were: DFS 76% and 50%, local control 84% and 64%, severe complications 19%.

PELVIS Seventy five children or adolescents were treated by a multidisciplinary approach including brachytherapy. These pelvic tumors are divided into: anal canal tumours, bladder-prostatic tumours, gynecological tumours.

Anus: only 3 patients received interstitial brachytherapy, 1 case as first line treatment, 2 cases as salvage treatment. Two out of three patients are alive.

Bladder-prostate (15 patients): Intraoperative brachytherapy was indicated as first line treatment in 12 and as a salvage in procedure 3. In the first group, the 3-year DFS is 75% with a conservative treatment in 8 of 9 patients alive; in the second group, only 1 patient is cured.

Gynaecological tumours: this tumour site must be divided into two main groups according to the pathological distribution:

- *sarcoma and yolk sac tumours*: a total of 30 patients: 5 stage IB (FIGO classification), 7 stage II, 10 stage III, 2 stage IV and 6 with recurrences. The 5-year DFS was obtained in 83% of cases, with a local control rate of 90% but near 30% of grade 2 and 3 complications.

– *clear cell adenocarcinoma:* thirty two young patients have been treated in the Gustave-Roussy brachytherapy department, but only twenty eight with a follow-up more than 2 years are reported. DES exposure was found in 64% of cases. The FIGO stage distribution was 6 IB, 8 II, 8 III, 6 IVB. The 2-year DFS rate is 71% with 20% grade 3 complications. A conservative approach preserving ovaries, uterus and vagina, was possible in 20 patients, one of them giving birth to a normal child, 5 years after treatment.

LITERATURE REVIEW *Zelefsky and colleagues* (2) reported the experience of MSKCC on 22 children treated with a combination of surgery and brachytherapy for soft tissue sarcomas. Iodine 125 was used in 7 cases, Ir 192 in 15 cases. The different tumor locations were: extremities in 16, trunk in 4 and orbit in 2. Half of the patients had recurrent lesions at the time of brachytherapy. In 68% of cases margins were positive. The results are quite encouraging despite bad prognostic factors: 5-year actuarial overall survival 87%, local control 68% (95% inside implanted volume), no severe complications.

Fontanesi et al. (3-4) has reported the SJCRH experience about 58 pediatric patients implanted in 62 sites including 10 retinoblastomas (non included in our own study). Brachytherapy was the only radiation treatment given in 11 patients, boost brachytherapy was indicated for recurrent disease or second tumor in a previously irradiated area. The disease free survival was 75%, the local control 86%, the complication rate 26%.

Curran and associates (5) published his experience on 12 children who received brachytherapy for soft tissue sarcoma. Brachytherapy was used as first line in a multidisciplinary treatment in 8 cases, and in 4 cases as salvage procedure. The radionuclides used were Iridium 192: 9 times, Iodine 125: 2 times and Californium 252: once. Six children presented with HAN tumors, 4 with pelvic tumors, 1 with extremity sarcoma, and another one with a retroperitoneal tumor. For this group (first line treatment), 7 out of 8 children have maintained local control; in the second group, only 1 out of 4 did so. Complication rate at 2 years was minimal.

Other experiences were also published but the cases were few in each series. *Martinez et al.* (6), *Plowman et al.* (1), *La Quaglia et al.* (7), *Cherlow et al.* (8), *Lewis* (9), *Neckuskin et al.* (10) and *Marques et al.* (11) have published same encouraging results emphasizing the good local control and minor sequelae obtained by brachytherapy when compared with external beam irradiation.

HDR brachytherapy was performed in some cases and the largest experience in this field is that of *Nag* (12-14). He prefers HDR to LDR brachytherapy as he thinks that LDR brachytherapy is often not practicable in children, because of poor tolerance during the hospitalization, and also because the risk of radiation exposure to personal and the child's family. Seven children (2 head and neck, 4 pelvic, 1 chest wall) were treated by *Nag et al.* (12-14) in a multidisciplinary treatment using HDR brachytherapy. The catheters were implanted intraoperatively in 5 patients and in the last 2 patients a custom-made vaginal applicator was used. At 2 years all children are alive, acute reactions look acceptable; however it may be too early to evaluate late sequelae.

CONCLUSION In childhood oncology brachytherapy can play an effective role if it is integrated in a multidisciplinary approach, if it is based on precise and exact standards and on the use of modern brachytherapy in adult patients.

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Adjuvant radiation therapy in gynecologic malignancy

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INTRODUCTION Radiation therapy is used in most gynecologic malignancies, either as the primary therapeutic modality or as an adjuvant to attempt to improve the local control and survival of patients who are diagnosed with these lesions. The role of radiation is particularly important as a therapeutic modality in cervical, vaginal, vulvar and endometrial cancer, and these will be discussed below. The role of radiation in the treatment of patients with most ovarian cancers is not as clear, and this issue will not be reviewed.

RADIATION THERAPY FOR CERVICAL CANCER

STAGE IB/IIA CANCER

RADIATION THERAPY AFTER RADICAL HYSTERECTOMY The value of adjuvant postoperative pelvic irradiation following radical hysterectomy is unproven. While postoperative irradiation in these patients has been shown to be associated with a lower subsequent rate of pelvic recurrences, the impact on survival remains uncertain (1-5).

Adjuvant radiation is typically administered to patients with high-risk findings determined at the time of laparotomy and hysterectomy. These features include histopathological findings such as the presence of pelvic lymph node metastasis, the finding of deep or extensive stromal invasion, positive surgical margins and parametrial spread (1-5). However, the patients analyzed in these studies were selected for their high risk features, and it is difficult to determine whether adjuvant radiation had an impact on survival. Interestingly, in a study by *Kinney et al.* (6), a retrospective comparison of two groups each of 60 age-matched patients with Stages IB and IIA cervical cancer (one group received adjuvant postoperative pelvic radiation therapy and the other did not), there was a lower pelvic failure rate in the irradiated patients, but no apparent impact on survival. However, the tumors were characterized only on the basis of tumor size, number and site of positive nodes. While it has been suggested the postoperative irradiation may not work as well as primary irradiation in patients whose tumors have high-risk variables, this has not been proven (7).

High energy photons (15-18 MV) are generally preferred because they better spare the normal tissues (8-9). Using these high energies, the pelvis can be treated using the four-field technique or a anterior-posterior technique. With lower energies (4-6 MV) the four-field technique should be used to minimize the risk of damage to the normal tissues. A major concern has been that irradiation after radical pelvic surgery may be too morbid.

The data from most studies are difficult to interpret because there are either too few patients or inconsistencies in the method of analysis (10-14). While some authors have reported a higher rate of postoperative intestinal obstruction, others have not. *Bandy et al.* (14) reported a higher rate of bladder dysfunction in those irradiated after hysterectomy compared with those only undergoing hysterectomy.

PRIMARY RADIATION THERAPY The use of a combination of external and internal pelvic radiation for patients with low-stage cervical cancer is highly effective (15-18). Pelvic control rates and long-term survivals are excellent, especially for those patients with small (less than 4 cm diameter) tumors. *Eifel et al.* (15) reported a 5-year disease-free survival rate of 90% for 701 patients with such stage Ib tumors, with a central tumor control rate of 99% and a pelvic control rate of 98%. The disease-free survival rates for patients with larger tumors is lower. For tumors 4 < 5 cm, the survival was 86%, and for those 5 cm or larger, 67%. Pelvic tumor control rates of 82% were achieved in the latter group. In other series, have confirmed these data. For stage IIA tumors, 5-year survivals of 70-85% have been reported, and the survivals correlate with tumor size.

The principal strategy for pelvic radiation therapy in cervical cancer is to achieve tumor and pelvic control, which includes eradication of the cervical disease, the parametrial disease, and sterilization of any metastatic disease to the pelvic lymph nodes.

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The general approach has been to combine external and internal irradiation to maximize the likehood of control and to minimize the risk of concomitant damage to the other pelvic viscera, particularly the bladder and bowel. The balance of dosing and techniques via internal and external radiation has been used by radiotherapists to customize the treatment based on the geometry and size of the primary tumor. Brachytherapy is an essential component in local tumor control. Small tumors usually require 80-85 Gy to point A, which may be reduced by 5-10% in small very small tumors. The field for the teletherapy is usually the whole pelvis, but for small tumors, the field size has often been made smaller, although the field covers all of the pelvic lymph nodes cephalad to the low common iliac lymph nodes (16, 17).

RADIATION FOLLOWED BY HYSTERECTOMY Some authors have suggested that the performance of an extrafascial hystectomy after the completion of pelvic radiation therapy might improve both local tumor control and survival of patients with "bulky" cervical cancers (19-23). In general, when this strategy is used, the total dose of pelvic irradiation is reduced by about 10% and the hysterectomy is performed about 6 weeks later. The purpose of waiting that interval is to permit the maximum amount of tumor shrinkage prior to hysterectomy. Radical hysterectomy is usually avoided because of the increase in the morbidity, particularly to the lower urinary tract (24-25).

In a report from the M.D. Anderson Hospital in 1968, *Durrance et al.* (19) presented data that appeared to show that patients with "bulky" tumors (6 cm or larger) had a better local control rate and survival when their pelvic irradiation was followed several weeks later by the performance of an adjunctive hysterectomy. These patients were compared with those who had received pelvic irradiation only. However, in a 1992 update of that experience, *Thoms et al.* (20) reported that the differences seen in the prior experience may have resulted from the preferential use of radiation only in tumors that were very large, especially larger than 8 cm in diameter. The survival excluding these patients was essentially the same.

Mendenhall et al. (21) reported no defference in both pelvic tumor and survival rates for patients with tumors measuring 6 cm or larger when treated with either radiation or radiation followed by hysterectomy. The central recurrence rate for tumors 7-8 cm in the M.D. Anderson patients was less than 10% in patients treated with >80 Gy to point A and no hystectomy was performed (15, 22).

Therefore, the recent retrospective data do not indicate a benefit of adjunctive hystectomy in these patients (23). The Gynecologic Oncology Group recently completed a prospective randomized trial of pelvic irradiation with or without adjunctive hysterectomy in patients with tumors 4 cm or larger, and hopefully an analysis of these data will provide the answer to the question.

STAGES IIB-IVA Radiation therapy is the primary treatment for patients with stages IIb through IVb cervical cancer (26-31). The results depend on the appropriate use of the combination of teletherapy and brachytherapy so that the dose of therapy can be optimized for control of locoregional disease and preservation of normal tissues. In general, breaks during treatment should be avoided and best results have been achieved when the irradiation has been completed in 7-8 weeks (26).

THE ROLE OF PARAAORTIC IRRADIATION The role of extended field radiation in the treatment of cancer of the cervix is unclear. In summary, most of the series that report patients who underwent a surgical staging indicate that approximately 10-15% of patients with clinical stages Ib to IIIb have evidence of lymph node metastases to the paraaortic lymph nodes at the time of a "surgical staging" operation (27-31). Five year disease-free survivals of up to 20-25% have been noted in some patients with microscopic metastases whereas those with macroscopic lymphadenopathy have approximately a 10-15% survival after extended field radiation (32-39). The survival is also correlated with the size of the central pelvic tumor. In patients who have been explored for radical hysterectomy and the operation was aborted because microscopic lymph node metastases were found in the low paraaortic area, the subsequent five-year survival rate was 48% in those patients receiving extended field radiation (39). This experience also demonstrates that some of these patients can be cured and supports the notion of surgical staging for patients with bulky, central disease even when preoperative CT scans are negative.

Two randomized prospective trials have studied the role of prophylactic paraaortic radiation in patients without known paraaortic involvement. In a study conducted by the Radiation Therapy Oncology Group, 367 patients with stages Ib, IIa (larger than 4 cm in diameter) or stage IIb tumors were randomized to receive either standard pelvic radiation or extended field radiotherapy prior to these cesium implants (40). For the 337 evaluable patients, survival was significantly better for those treated with extended field radiation compared to the standard pelvic radiotherapy (67% versus 55%). In a second trial from the European Organization for the Research and Treatment of Cancer (EORTC), the patients included in the study were patients with stage I and non-bulky IIb with positive pelvic lymph nodes on lymphangiogram or surgery and bulky stages IIb and III (41). The four year disease-free survival rates were not significantly different in those treated with extended field versus pelvic radiation therapy. The rate of paraaortic node recurrence was significantly higher in the patients treated with pelvic irradiation only and in those where local control was achieved. The rate of distant metastases was 2.8 times greater if treatment was with pelvic irradiation only. Both studies documented an increased rate of enteric complications in patients treated with extended field radiation therapy. In the EORTC study, most small bowel obstructions occurred in patients who had undergone a transperitoneal operative staging. Although the morbidity of extended field radiation is no longer prohibitive with multiple field techniques, it is still higher than that seen with standard pelvic irradiation therapy. The role of prophylactic paraaortic radiation, therefore, remains

undefined. Better studies need to be conducted and there needs to be further refinements in treatment.

INTERSTITIAL BRACHYTHERAPY The use of interstitial brachytherapy to treat patients with cervical cancer, especially those with tumor volume and distribution that makes it difficult to get a good intracavitary placement, has been advocated by several authors. Interstitial implants are typically placed transperineally (42-48). Multiple needles are inserted through a lucite template which permits parallel placement of small bone needles that penetrate the cervix and the paracervical tissues. The usual source is a irridium 192. Initial reports were very enthusiastic and described a major potential advantage of this approach. However, there have been very few reports of long-term survival in patients treated with interstitial brachytherapy for primary cervical cancer. Although initial data from *Syed* (47) and *Martinez* (46) suggested five year survival rates of 53% for patients with IIIb disease and local control rates in excess of 80% for patients with IIb to IIIb disease, recent data from Stanford and the Joint Center for Radiation Therapy at Harvard been disappointing (48). The three year disease free survival rate for stages IIb and IIIb were 36% and 18%, respectively, with local control rates of 22% and 14%, respectively. Furthermore, the rate of complication requiring surgical intervention was high. Therefore, in general, the use of interstitial treatment for primary cervical cancer should probably limited to patients who cannot be treated acceptably with interuterine brachytherapy.

BRACHYTHERAPY DOSE RATE Attempts have been undertaken to increase the dose rate of brachytherapy to minimize the duration of hospitalization required to deliver the appropriate dose. In general, an increase in dose rate may theoretically compromise the therapeutic ratio (49). While computer technology has made it possible to deliver brachytherapy at very high dose rates (greater than 100 cGy per minute). The potential loss of radiobiologic advantage over the low dose treatment are a concern. Thusfar, studies have not conclusively shown this to be a benefit and approach remains experimental and controversial.

COMPLICATIONS OF PELVIC RADIOTHERAPY FOR CERVICAL CANCER Gastrointestinal symptoms following pelvic radiotherapy for cervical cancer are common (50-53). Most patients experience at least mild to moderate intermittent diarrhea lasting for a period of often 1-3 months. Bladder irritation or "radiation cystitis" is also very common in these patients. Patients who undergo extended field treatment have significant nausea, gastric irritation as well as anemia are rather common. The use of concomitant chemotherapy in these patients increases the side effects. All treatment of patients who receive pelvic radiotherapy will experience ovarian failure by the completion of treatment. As approximately 800-1000 cGy will virtually eliminate ovarian function. Ovarian failure can sometimes be obviated by the performance of an ovarian transposition operation.

Complications of intracavitary therapy include uterine perforation, infection, and the risk of anesthesia as well as thromboembolic disease from temporary immobilization (50). Thromboembolic complications fortunately are not common (<2%) and pulmonary embolism is even less often, less than 0.2%.

Late complications from the combination of brachytherapy and external beam therapy for cervical cancer vary considerably in the literature reports. However, most reports indicate that there is an overall risk of major complications, i.e, those that require hospitalization or surgery or transfusion of somewhere between 5 and 15% (53).

THE USE OF CONCOMITANT CHEMOTHERAPY AS RADIATION SENSITIZERS A variety of data indicate that the use of concomitant chemotherapy as a radiation sensitizer is useful for the control of central pelvic disease (54-57). 5-FU given continuously for 4-5 days for 2-3 times during treatment with or without bolus cisplatin has been used and shown to be reasonably well tolerated. It is unclear if such an approach ultimately results in improvements of disease progression free and absolute survival. Randomized comparisons of hydroxyurea versus 5-FU and cisplatin are being performed by the Gynecologic Oncology Group and the data should be available for review in the not too distant future. There is no evidence that the use of radiation sensitizers improves the outcome in patients with microscopic metastases to the pelvic lymph nodes although this is also the subject of the GOG study.

TREATMENT AFTER SIMPLE HYSTERECTOMY WITH UNSUSPECTED INVASIVE CANCER Occasionally an extrafascial hysterectomy is performed on patients who have unsuspected cancer and the determination has been made based on the final pathology evaluation of an invasive cancer exist (58-62). Patients may be classified according to the disease, the extent of disease at the time of initiation of radiation therapy into the following groups:

1. micro-invasive cancer,
2. tumor confined to the cervix with surgical margins negative,
3. surgical margins positive but no gross residual,
4. gross residual tumor by a clinical examination documented by biopsy, and
5. patients referred for treatment more than six months after hysterectomy, usually for recurrent disease.

In a report analyzing the subgroups, *Roman et al.* (58) substantiated survival rates of 79% for group 2, 59% for group 3, and 41% for groups 4 and 5 (62).

Patients with micro-invasive carcinoma without lymph-vascular channel involvement require no adjuvant chemotherapy. Those with more extensive disease and negative margins should be treated with 45-50 Gy of pelvic radiotherapy plus a vaginal intracavitary therapy with an additional 30-50 Gy to the vaginal surface. In patients from groups 4 and 5, 65 Gy of external beam therapy with or without intracavitary radiation therapy should be used (61-62).

CARCINOMA OF THE CERVICAL STUMP Supracervical hysterectomy use to be a popular operation until the 1950s and then, indeed, carcinoma of the cervical stump was a relatively common event. The performance of this operation declined considerably until the recent few years as did the incidence of cervical stump carcinoma. Because of the renewed popularity of this operation, there is a possibility that we may again see an increase in the disease.

Very small tumors can be treated with trachelectomy (63-64). Patients with Ia1 disease can undergo a simple trachelectomy versus those with Ia2 of Ib undergoing radical trachelectomy with pelvic lymph node dissection. This might be a choice for very young patients who wish to preserve ovarian function. However, within a larger disease, combination of external beam and brachytherapy is necessary. If the remaining endocervix is two or more centimeters in length, a small intracavitary insertion may be possible depending on the length of the endocervical canal. Appropriate placement of vaginal ovoids can also help to provide appropriate brachytherapy in these patients (65-66). The treatment must be customize with external beam therapy modified depending on the extent of brachytherapy permitted. Most patients who have inadequate endocervical canals, vaginal ovoids are not adequate to provide sufficient brachytherapy and the patient must be treated primarily with external beam therapy.

Fortunately, the survivals for such patients carefully analyzed seem to be very close to the those patients with carcinomas of the intact cervix. Most authors have not reported an increase in morbidity associated with this operation compared to patients with carcinoma of the intact cervix (63, 66).

INVASIVE CANCER OF THE VAGINA

INTRODUCTION Radiation is the treatment of choice for most vaginal cancers because it is usually not possible to obtain adequate surgical margins even with very small tumors (67-79). Furthermore, the distribution of tumors such that stages II and III are more common.

STAGE I Surgery has a limited role in the treatment of stage I disease (69-70, 73-74). Early tumor that involve the upper posterior vagina can be treated similar to early invasive cervical cancer with a radical hysterectomy and proximal vaginectomy in those patients who have a uterus or in a radical proximal vaginectomy in those who have undergone a prior hysterectomy. In general, a bilateral pelvic lymphadenectomy is performed concomitant with these procedures. The five year survival rate for patients so treated is in the range of 56-80% (71-72).

Definitive irradiation for stage I disease is highly effective with survival rates of 75-95% (67, 71). In some early cases with superficial tumors, brachytherapy alone may be utilized. The recommended dose of 60-70 Gy calculated 5 mm beyond the plane of the implant or vaginal mucosa should be given. The vaginal surface dose is 80-120 Gy. Thicker stage I tumors should be treated with external beam and brachytherapy delivering 40-50 Gy to the pelvic nodes and 70-75 Gy to the tumor.

STAGE II Most patients with stage II disease require treatment of external beam irradiation and brachytherapy. Survival rates vary between 50-85% (72-73). These analyses are complicated by the fact that there is often variation in distinguishing the clinical stage I from clinical stage II and because of their variety of different treatment approaches.

Most situations require a "customized" management. Examination under anesthesia may be needed to determine whether intracavitary treatment will cover the tumor adequately. In patients who have an intact uterus, proximal vaginal fornix lesions can be treated with tandem and ovoids, while larger tumors may require a boost with interstitial therapy or external beam treatment. Brachytherapy in general is an important component of the treatment of these tumors and can be designed to treat the entire vaginal tumor. *Chyle et al.* (67) reported excellent control rates with primary brachytherapy for stage II disease.

Selected patients with stage II disease can be treated with radical surgery (69). However, because the procedure may require extensive resection of the parametria or even bladder, an exenteration may be necessary to cure these patients.

STAGES III AND IVA Disease III survival rates for this disease are 30-50% for stage III and 15-30% for stage IVa (67, 71, 72, 77). While pelvic recurrence rates following extensive radiation therapy are high, the rate of recurrent disease out of the pelvis is very high in these patients. All patients require external radiation therapy and brachytherapy whenever possible to "consolidate" the treatment. Clearly, brachytherapy is less useful when the tumor is very large and, therefore, more of the therapy must be delivered by external beam. In general, the concept is to try to "cytoreduce" the tumor with external beam followed by implant whenever possible. The total dose to the primary treatment should be 75-85 Gy.

RADIATION THERAPY FOR INVASIVE CARCINOMA OF THE VULVA

INTRODUCTION Most invasive carcinomas of the vulva are present in stage I and II and, therefore, are treated with radical or modified radical surgery (78-80). It is common now for patients with stages III and IV disease to be treated with radiotherapy with concurrent chemoradiation therapy in an effort to minimize the need for radical vulvectomy and pelvic exenteration to treat these patients (81-82).

STAGE I AND II Most patients with T1 and T2 lesions are treated with a modified radical vulvectomy (radical local excision) (78). In patients with disease invasive to >1 mm, at least ipsilateral inguinal femoral lymphadenectomy is performed in the vast majority of patients. Radiation therapy to the groin or pelvis

are reserved for those uncommon patients with metastases to the regional lymph nodes. Lymph node metastases in patients with stage I disease are seen in no more than 5-10% of patients and in up to 15% in patients with stage II disease (78-81).

Post-operative of radiation to the vulva alone is occasionally used when margins of the surgical resection are close (<8 mm) in those patients with negative inguinal femoral nodes (83, 83). An alternative is re-resection of the area.

In patients with positive lymph nodes, a dose of 50-65 Gy is usual given to the pelvis. In patients with positive margin, an appositional perineal electronic beam field can be used or the an interstitial implant can be used (85-89).

STAGE III AND IV Patients with T3 and T4 lesions, that is, primary tumors that involve the anus, rectum, rectal vaginal septum or proximal urethra, obtaining an adequate surgical margin is difficult without a pelvic exenteration combined with a radical vulvectomy and bilateral inguinal femoral lymphadenectomy. Furthermore, the morbidity of the ultraradical surgery is considerable though all these patients get one breakdown and may require a prolonged hospitalization. Therefore, any effort to be "conservative" of the vulva tissue is warranted.

Several authors have now indicated that combination of radiation with concomitant chemotherapy is the primary choice for such advanced lesions (81-82). The use of preoperative irradiation permits considerable shrinkage in most patients thus minimizing the need for more extensive surgery. In some patient with T3 tumors initial vulvectomy can be performed without sacrificing major organ function and postoperative radiation can be given particularly if margins are close. In patients with large T3 and T4 lesions, preoperative radiation to 45-55 Gy permits considerable shrinkage and a less radical operation. The outcome of such patients may, in fact, be better than patients undergoing more radical operations with survivals of stage III approximating 70% and close to 50% or 60% in stage IV. This experience compares favorably with historical data for radical surgery of 50% and 25%, respectively, for stages III and IV disease.

ELECTIVE REGIONAL RADIATION OF VULVAR CANCER In the past, pelvic node dissection was performed on all patients with invasive cancer. Subsequently however, it has been demonstrated that pelvic node metastases are found only in patients with multiple positive inguinal nodes so the operation was limited to this group of patients. However, in 1986, the GOG data were published (90). This study was a randomized prospective study that compared pelvic node dissection with inguinal and pelvic irradiation in patients with inguinal node positive squamous carcinoma of the vulva. The study closed prematurely because there was a survival advantage for the patients treated with radiation therapy to the pelvis. All patients had been initially treated with radical vulvectomy and inguinal lymphadenectomy and randomization was performed intraoperatively after frozen section evaluation of the inguinal lymph nodes. There was a marked difference in survival of patients with clinically positive or multiple histologic positive nodes. For those patients with two or more positive inguinal lymph nodes, the two-year survival rates were 63% in the radiation group and 37% for the pelvic node group. This study permitted the discontinuation of the pelvic lymphadenectomy for patients with positive inguinal-femoral lymph nodes documented at the time of vulvectomy for invasive vulvar cancer.

It has been proposed that radiation to the groin would be a suitable alternative to the performance of the inguinal lymphadenectomy for patients with low stage vulva cancer. In 1992, the Gynecologic Oncology Group reported the results of a trial which randomly assigned such patients with clinically negative inguinal femoral nodes to receive either irradiation versus lymphadenectomy (91). The study was closed prematurely because an interim analysis demonstrated a significantly higher rate of inguinal recurrence and death in the irradiated group. Patients were treated with anterior appositional fields with the dose prescribed at 3 cm in depth. The problem with this trial is that some inguinal-femoral nodes extend to a depth of 5-8 cm and this may explain why this treatment was unsuccessful. Thus, the use of this approach, i,e, groin irradiation in lieu of inguinal femoral lymphadenectomy, remains controversial and requires further study.

ADJUVANT RADIATION THERAPY FOR ENDOMETRIAL CANCER

STAGE I Adjuvant radiation has not been shown to improve survival for patients with endometrial cancer. However, because most patients with stage I disease have an excellent prognosis following surgical extrication of their primary disease, it has been difficult to prove the value of postoperative radiation therapy (92-98). Radiation has been shown to significantly decrease the incidence of both pelvic and vaginal recurrences and, therefore, logically it should improve survival for selected high risk patients (95-97). The use of preoperative irradiation versus postoperative adjuvant radiation therapy remains controversial and patterns of treatment vary according to different centers. Most centers in North America now recommend postoperative adjuvant therapy because surgical therapy allows the more definitive determination of the radiation field, e.g., if extended field radiation therapy to be used. Indeed, this approach does allow "customized" management with only selected patients receiving adjuvant therapy.

Vaginal vault recurrences can be decrease by either external irradiation or intracavitary radium (92, 94). Pelvic recurrences may be decreased by external radiation (95-97). Another potential benefit of radiation to the pelvis postoperatively is the ability to resect grossly enlarged nodes which may theoretically enhanced the likelihood of regional control with adjuvant pelvic irradiation. About 5000 Gy is probably necessary to sterilize microscopic metastases in lymph nodes and this approach could facilitate an improved outcome.

Prior to the use of surgical staging for endometrial cancer, preoperative intracavitary plus external irradiation was usually given (94, 97). The rationale for this approach was that radiation would "sterilize" the malignant cells, potentially decreasing the likelihood of vaginal implantation or systemic metastases during the time of uterine manipulation. In general, such theories have not been proven, however. It is likely that vaginal recurrences are due to lymphatic spread which takes place prior to any surgical manipulation. Data from a variety of studies also suggest that "manipulation" associated with intracavitary therapy or surgery is not associated with a higher risk of disseminated disease (98). Although there are no clear randomized prospective data in this regard, it is unlikely that primary surgery is associated with tumor dissemination.

The main argument for performing surgery prior to radiation is that a significant number of patients will be found to have "good prognosis tumors", i.e., without evidence of spread such that adjuvant radiation therapy can be safely eliminated. For those patients who require postoperative radiation, the therapy can be better tailored to the individual patient, the extent of disease based on appropriate surgical staging.

VAGINAL RADIATION Vaginal recurrence, in general, carries a poor prognosis, and intracavitary vaginal radiation can be used to significantly reduce the incidence of vault recurrence (92-101). In an important study by *Lotocki et al.* (92), the use of either preoperative or postoperative vault radium decreased the incidence of vault recurrence from 14% to 1.7%. In general, the morbidity of this approach is low, although vaginal stenosis and dyspareunia may be a problem in postmenopausal patients in the absence of vaginal dilation.

The treatment approach for vaginal vault radiation is the use of colpostat alone to deliver a surface dose of 55-60 Gy. Vault cesium alone can be used after surgical staging for patients with relatively low risk, e.g., grade 2 disease and negative lymph nodes. While pelvic lymphadenectomy for staging alone is likely not as good as the removal of enlarged nodes followed by external irradiation, this approach does allow the omission of external radiation therapy in many patients.

EXTERNAL PELVIC RADIATION The use of surgical staging has increased the number of patients in cancer centers undergoing pelvic lymphadenectomy (102-106). This approach has, in fact, decreased the number of patients requiring external pelvic radiation. Because external pelvic radiation can significantly decrease the risk of pelvic recurrence, high risk patients who have not undergone surgical staging should receive such treatment. These patients include all those with poorly differentiated tumors and those that have invaded to beyond the middle third of the uterus. Patients who have multiple positive pelvic node metastases are at significant risk of aortic node metastases. Therefore, a treatment option is to give those patients extended-field irradiation, that is, both pelvic and paraaortic irradiation, unless the paraaortic lymph nodes have been dissected and proven to be negative.

External pelvic irradiation should be as effective as vaginal vault radiation to sterilize central pelvic disease. Therefore, it is not necessary to administer both external irradiation and vault irradiation postoperatively as the morbidity will be significantly increased. *Stokes et al.* (104) reported a serious complication rate of 8.8% when both external radiation and intracavitary radium were combined. In another study at the Radiumhemmet (105), the incidence of late complications in the group receiving postoperatively external irradiation was 1.8% compared with 15.9% in the group receiving both external and internal irradiation.

EXTENDED FIELD RADIATION The same risk factors that indicate the likelihood of pelvic lymph node metastases also puts the patient at risk for paraaortic lymph node metastases. In patients undergoing pelvic radiation alone, failure rates of 15-20% have been reported, subsequently, in the paraaortic lymph nodes (106-108). Recent data suggests that 40-45% of patients with confirmed metastases to the paraaortic lymph nodes who undergo extended field radiation (pelvic plus paraaortic external beam radiotherapy) are free of disease at 5 years. (109). The indication for such treatment would be biopsy proven paraaortic lymph node metastases, grossly positive pelvic nodes, and multiple positive pelvic nodes especially in those patients who had not undergone a paraaortic lymphadenectomy, those patients with grossly positive adnexal metastases and those with deeply invasive, poorly differentiated tumors. A study administering extended field radiation therapy to those patients with positive pelvic nodes only in the absence of paraaortic lymphadenectomy has not been reported, however.

The morbidity of extended field radiation is clearly greater than that of pelvic irradiation alone. However, *Potish et al.* (109) reported only one case of severe enteric morbidity in 48 patients for a complication rate of 2% using paraaortic irradiation of 45-50 Gy.

WHOLE ABDOMINAL RADIATION The use of whole abdominal radiation therapy for endometrial cancer has been limited and controversial. In the past, it has been used for patients with positive peritoneal washings or adnexal or peritoneal metastases (110). However, most studies have not analyzed their patients by tumor histology. There are no randomized data of whole abdominal radiation therapy in such unselected patients and, therefore, its role in these individuals is controversial.

Most recently, radiation therapy has been used to treat patients with papillary serous carcinoma of the endometrium particularly those at high risk to recur in the upper abdomen. This approach is analogous to the treatment of stage IIIa epithelial ovarian cancer of the serous type. While it is theoretically possible that whole abdominal radiation therapy may prove useful in this group of patients, so might the use of adjuvant systemic chemotherapy (such as cisplatin and paclitaxel) and a randomized comparative trial might be necessary to address this question.

INTRAPERITONEAL ^{32}P Intraperitoneal ^{32}P has been used in the past in patients with malignant peritoneal cytology. Some favorable results have been reported in the past in retrospective analysis (111). Because patients with positive peritoneal cytology are also at risk for vaginal and pelvic recurrence, they generally require external pelvic radiation as well. The combination of intraperitoneal chronic phosphate and external beam pelvic radiation therapy is associated with a high chronic intestinal morbidity, however, and therefore, this approach probably should be avoided.

The significance of positive peritoneal washings as an independent variable remains controversial. *Milosevic et al.* (112) in a retrospective review of the literature suggested that adjuvant therapy for patients with malignant cytology as their primary adverse predictor of outcome should not be given routine adjuvant radiotherapy. Other adverse prognostic factors alone they suggest should dictate the use of adjuvant treatment. Thus, the role of ^{32}P in these patients remains controversial.

STAGE II In patients who have both endometrial and cervical cancer involved with adenocarcinoma, it may be difficult to distinguish between stage Ib adenocarcinoma of the cervix and stage II endometrial cancer (113-116). Clinically, when the cervix is not enlarged and there is a positive endocervical curettage, this most likely represents a "false positive" assessment of the cervix and, therefore, use of preoperative irradiation to the cervix in these patients would likely represent over treatment. In patients with clinically expanded cervixes, the diagnosis can be difficult. The retrospective analysis of this subject have generally been nonrandomized and, therefore, inclusive. However, patients with stage II endometrial carcinoma have about a 35% incidence of positive pelvic lymph nodes and, therefore, pelvic irradiation therapy remains the standard treatment for these patients (113).

There are two main approaches for the treatments of patients with stage II endometrial cancer, that is, either 1) radical hysterectomy with bilateral pelvic and paraaortic lymphadenectomy, or 2) combined radiation and surgery, generally preoperative external pelvic irradiation and an intracavitary cesium followed in six weeks by a total abdominal hysterectomy, bilateral salpingo-oophorectomy.

The most common approach used in patients with stage II disease is external and internal cavity radiation followed by extrafascial hysterectomy. The hysterectomy is usually performed about six weeks after the completion of the radiation therapy to allow the inflammatory edema to subside. Preoperative external radiation of the cervix may optimize the geometry for the intracavitary insertion. Using this approach, *Bruckman et al.* (117) treated with 25 patients with 40 Gy whole pelvis radiation and 4000 mg hours intracavitary radium with a single insertion. In this group there were no vaginal recurrences and all patients with pelvic recurrence also had distant metastases. *Nahhas et al.* (118) reported no improvement in survival when radical hysterectomy was performed after the external therapy compared with patients who underwent intracavitary radiation plus extrafascial hysterectomy.

Combination therapy such as this in these in patients is associated with significant intestinal morbidity in the range of about 5-15%. Rectovaginal fistula may also develop in such patients.

Radiation therapy alone should be reserved for patients with medical contraindications to surgery, and although it may provide good pelvic control in patients with minimal myometrial invasion, those with more poorly differentiated tumors or more deeply invasive disease have a higher likelihood of central and distant failure.

The benefit of performing primary surgery on patients with apparent stage II disease, again, is that it allows more accurate assessment of the true extent of the disease. A modified radical hysterectomy can be performed along with pelvic and paraaortic lymphadenectomy and a full staging laparotomy. Following this, adjuvant radiation therapy can be given to all of the appropriate sites. Extended field radiation can be used selectively for those patients who are most likely to benefit.

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The role of radiation therapy in the management of the cancer of the vulva

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INTRODUCTION The role of radiation therapy in the gynecologic literature has been traditionally considered as not cost/benefit efficient. The reasons for such judgement were based in the poor results obtained with ortho-voltage techniques (1-4) with 5 years survival rates between 13 to 25 %and the reports of the severe complications following vulvar radiation therapy(5). The reluctance to use radiation were also based in the good results obtained with radical surgery alone and the fear to increase lymphedema if radiation was used adjunct to radical surgery. Nobody can deny the cure potential of radiation therapy in head and neck squamous cell carcinomas where dose control data assures that a dose of 4500 cGy in 5 weeks will sterilize 90% of nodal subclinical metastases and 6500 cGy will sterilize tumor masses up to 3 cm in size (6).

It is probable that vulvar cancer is as radiosensitive as other epidermoid cancers. Since the introduction of megavoltage therapy many reports of good results from small numbers of advanced vulvar cancers have been reported. An important argument against radiotherapy has been the moist desquamation produced after 2 weeks of vulvar irradiation.This is a result of the great number of blood vessels and appears after low doses of radiation are surpassed. Nowdays this complication is considerd unavoidable but with good care and suspension of treatment for certain days is a transient complaint.

Radiation therapy in vulvar cancer can be used :
1. Alone as primary treatment.
2. In advanced vulvar cancer alone or combined with surgery and/or chemotherapy to avoid exenteration and treat recurrences.
3. In vulvar cancer treated with radical surgery to improve survival when groin nodes are positive.

The purpose of these state of the art updating is to refresh the available data to help to take therapeutic decisions.

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RADIATION THERAPY AS PRIMARY TREATMENT OF VULVAR CANCER The best example of an institution that treated vulvar cancer with radiation alone is the Department of Radiologic Gynecology of the Womens University Hospital in Hamburg. *Frischbier et al.* (7) treated 446 cases from 1965 till 1983, with a 5-year survival of 47.8%. The survival of stages I and II was 53.0% and the survival of stages III and IV 37.3 %. The whole vulva was irradiated with electrons of 9 and 18 MeV supplied by a 19 MeV betatron. Single doses of 2.5-3 Gy five times a week. Total maximal dose was 45-60 Gy. For the nodes 45 Gy at about 3cm depth were given. A maximum dose of 60 Gy was given to suspicious nodes. Severe complications (ulcer, abcess, etc.) were observed in 42 patients (10.9%). Six had necrosis of the pubic bone, two stenosis of the urethra, three rectal stenosis. In stage II and IV serious complications were 12% and in stages I-II 9%. They conclude that biopsies should no be performed in vulvar cancers after radiotherapy and that radiotherapy is not the first choice for the treatment of vulvar cancer.

RADIOTHERAPY ALONE OR COMBINED WITH SURGERY AND/OR CHEMOTHERAPY TO AVOID EXENTERATION IN ADVANCED VULVAR CANCER AND RECURRENCES First it is important to consider the different definitions of advanced vulvar cancer. For *Hacker and Bereck* (8) when there is involvement of anus, rectum, rectovaginal septum and/or proximal urethra. According to *Lupi et al.* (9) locally advanced or inoperable vulvar cancer is found when size and/or site of the tumor hampers the possibility of excising it with free surgical margins and reasonable morbidity. For *Thomas et al.* (10) advanced disease is present when palpable inguinal nodes are suspected of containing tumor, or radical excision of the vulvar tumor will require sphincter sacrifice.

In *Frischbier et al.* (7) it was already mentioned that the results of 242 patients, stages III-IV treated with radiation alone had 37.3% of survival rate. *Backstrom et al.* (11) in T4 tumors treated with cobalt radiation the survival was 30% with a reported 12% of serious complications. *Acosta et al.* (12) gave properative irradiation followed by radical surgery in some stage III cases with good results. *Hacker et al.* (13) report 8 cases with advanced vulvar cancer in whom curative

surgery would have required pelvic exenteration. Preoperative irradiation in doses of 44 to 54 Gy in 37 to 49 days sterilized tumor in 4 of 8 patients. Local control was obtained in 6/8 and no patients required exenteration to clear tumor residual after irradiation.

Boronow (14) introduced in 1968 a combined individualized approach of radiation and surgery for advanced vulvar cancer and recurrences. It includes vaginal brachytherapy to treat the central extent of the disease and the associated lymphatic pathways for relatively low volume disease. Then external beam was used when the clinical volume of disease was felt to be too large for control with the vaginal radium. Finally radical vulvectomy with groin dissection at completion of radiation therapy, to complete treatment of the disease in the external genitalia. Brachytherapy was applied with Bloedorn or Delclos afterloading applicators and the dose vaginal surface ranged from 4500 to 10000 cGy. External beam is now used routinely. The results of 5-year survival were 75.6% for the primary cases and 62.5% for recurrent cases. Because of the fistulae *Boronow* (14) has reduced the maximum dose to 7000-8000 cGy from combined sources. The radicality of vulvectomies has also been significantly reduced. Thicker flaps, skin preservation and modified hemivulvectomies.

The great step forward in chemoradiation has been the experience of *Nigro* (15) using 5-fluoruracil and mitomycin C concurrent with radiation for cancer of the anus. This treatment achieved local control rates of 90 to 95% and virtually eliminated the necessity of abdominal perineal resection. These drugs act as radiosensitizers enhancing tumor cell kill. With chemoradiation some scarce experiences have been reported using the Nigro strategy or some variations of it. *Levine* (16) in 6 patients with good short terms results. *Thomas et al.* (17) treated 9 patients with a 66.6% complete response. *Berek et al.* (18) obtained complete response in 8 of 12 stage III and IV patients with cisplatinum and 5-FU. *Russel et al.* (19) reported the largest series of 18 patients treated with 5-FU and cisplatin with 78% alive with no evidence of disease at a median follow-up of 36 months. *Lupi et al.* (9) observed in 24 primary tumors (l9 of them stage III) an objective response in 22 (91.6%) with an adaptation of Nigro regime. After 2 weeks the patients had radical vulvectomy. Five of 9 patients with biopsy proven inguinal lymph nodes metastases showed no residual lymph node disease in the surgical specimen. Recurrence rate was 31.8% and the median follow-up time was 34 months.

It is good moment to defined certain strategies for radiation of the vulva and pelvic and groins nodes according to the *Toronto Bayview Regional Cancer Center* (10). In chemoradiation late fibrosis, atrophy, teleangiectasia, and necrosis are avoidable if the radiation fraction size is kept below 160 to 170 cGy and excessive total doses are not used. In recurrent disease it is recommended to achieve local control doses of >50 Gy. Also it is recommended doses of more than 55 Gy for macroscopic disease even when 5FU is used. The therapeutic window however may be narrow. They do not use doses in excess of 65 Gy to avoid morbidity. If residual disease persists after 55 to 65 Gy it can easily removed by local excision. For unifocal vulvar disease vulvar irradiation is delivered trough perineal portals localized to the site of the disease with appropiate margins as in surgery. No attempt should be made to irradiate the entire vulva unless required to encompass extensive disease. Postoperative pelvic irradiation for inguinal nodes involvement should have a superior margin limit of the radiation volume to the level of the midsacral joint, to avoid late bowel complications.

IN VULVAR CANCER TREATED WITH RADICAL SURGERY TO IMPROVE SURVIVAL WHEN GROIN NODES ARE POSITIVE Lymph node metastases is the most important prognostic factor in vulvar cancer in relation with 5-year survival. Negative nodes cases in spite of having extense primary tumors have a much better survival than small primary tumors with more than one positive groin node (8). The most important prospective randomized study is the GOG protocol 36 directed by *Homesley* (20). The objective of this study was to compare the survival of patients with positive groin nodes receiving either postoperative radiation therapy or surgery alone. Patients randomized for surgery were treated with ipsilateral or bilateral pelvic lymph node dissection depending on whether only one or both groins were found to have positive lymph nodes. Patients randomized for radiation therapy received 4500-5000 cGy midplane dose to the pelvis between the superior border of the obturator foramina and the L5-S1 interspace at a rate of 180-200 cGy per day. Radiation therapy encompassed both groins as well as the obturator, external, internal and iliac (pelvic) node areas. In 114 randomized patients, the 2-year relative survival was superior for patients receiving groin and pelvic radiation therapy (75%) after radical vulvectomy and bilateral groin dissection, compared with patients who were treated with surgery alone (56%) including an ipsilateral or bilateral pelvic lymph node dissection. The survival advantage was most dramatic in patients with more than one positive node metastases or with clinically suspicious or positive groin nodes. There was no advantage to those patients with occult metastasis and /or one positive node. Peripheral edema was 19% in the radiation group and 11% in the surgical group. These data strongly support the use of postoperative nodal radiotherapy at least for the identified subset of patients that have two or more micrometastasic groin nodes, macroscopic involvement of a single groin node or extracapsular disease extension. Many years ago the GOG protocol 88 tried to compare in a randomized way the possibility of replacing groin lymphadenectomy by radiation therapy, was discontinued because the radiation arm receiving 5000 cGy to a depth of 3 cm in the groin developed in 18.5% recurrences to the groins. To discover if methodologic errors were responsible of such failure, *McCall et al.* (23) measured in 100 women with CT scan, the depth of inguinofemoral nodes from the skin. Patients should not present adenopathies or prior inguinal surgery. The dose that would have been delivered to the inguinal lymph nodes of these patients was determined using isodose curves constructed

according to the guidelines in GOG protocol 88. More than the half of the patients would have received less than the 60% of the prescribed dose, because their inguinal lymph nodes were deeper than 5 cm, if the depth of their inguinal nodes had not been measured before therapy. This data open again the possibility of a new trial of GOG 88.

In recent years, new roads of research have been initiated in relation with special conditions of positive lymph nodes as prognostic factors. *Origoni et al.* (21) studied some characteristics of positive nodes in relation with survival.Metastasis of less than 5 mm in diameter have a survival of 90.9% ,with 5 to 15 mm of diameter 41.6% and with more than 15 mm it drops to 20.6%.

It is also stated that when lymph-node metastases are of intracapsular pattern, the survival is 85.7% and when they are extracapsular, drops to 25%. *Paladini et al.* (22) demonstrated that on multivariate analysis, extracapsular spread in lymph-node, metastasis is the most significant independent prognostic factor followed only by FIGO stage. Again for them, studying the same factors as *Origoni et al.* (21), 5-year survival was 51% in patients with intracapsular metastasis and if only one node showed extracapsular metastasic involvement 5-year survival dropped to 15%. For patients with only one positive node, the most important prognostic factor was the greatest dimension of the metastasis within the lymph node. Five-year survival was 83% in patients with metastasis occupying less than 5% of the node, and 17% in patients with metastasis involving more than 50% of the node. All this new refinements of the nodal prognostic factors should be confirmed but there is no doubt that will help to use adjuvant methods as radiation to offer better treatment to high risk patients (24) and at the same time will impact the FIGO staging classification.

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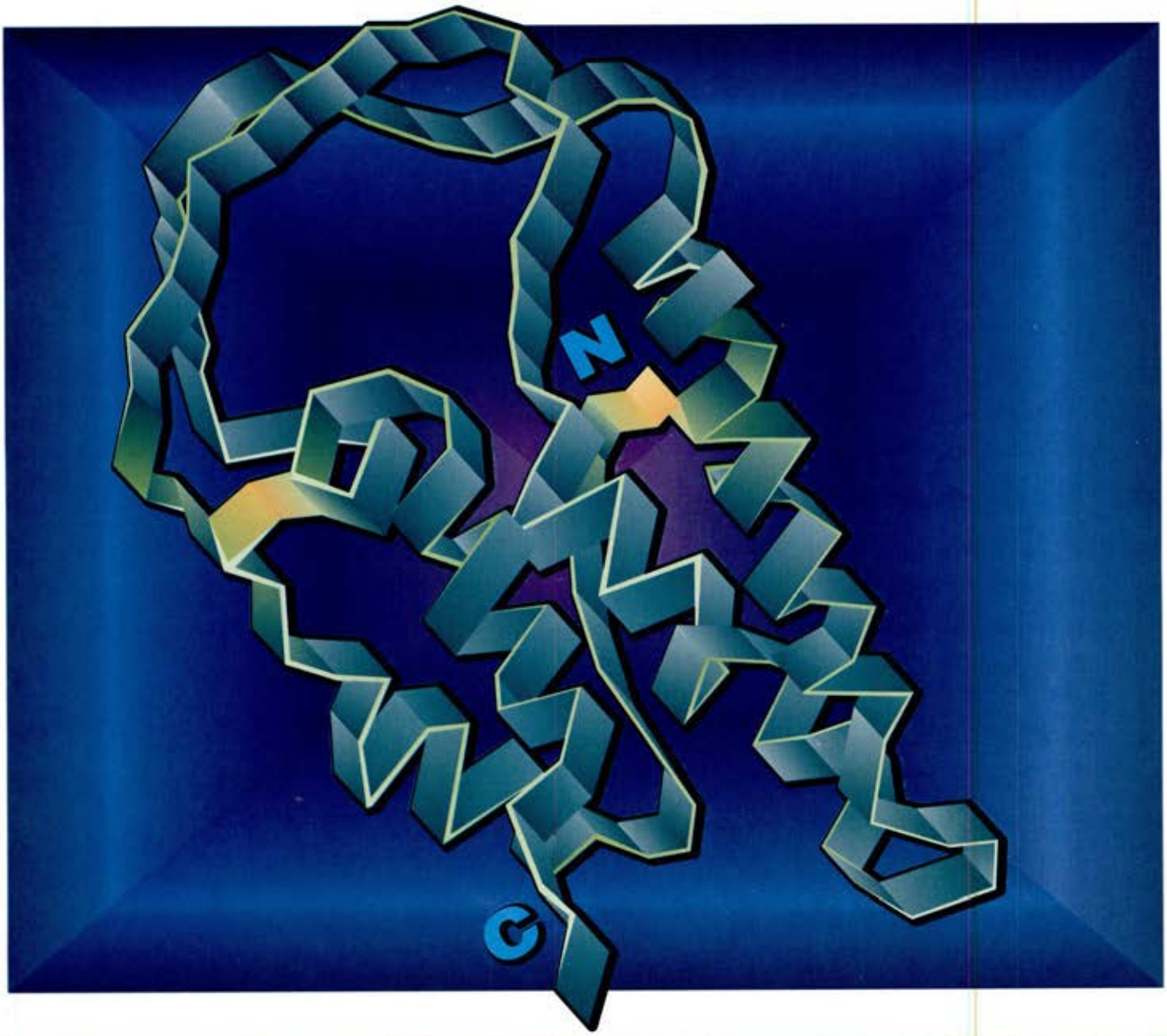

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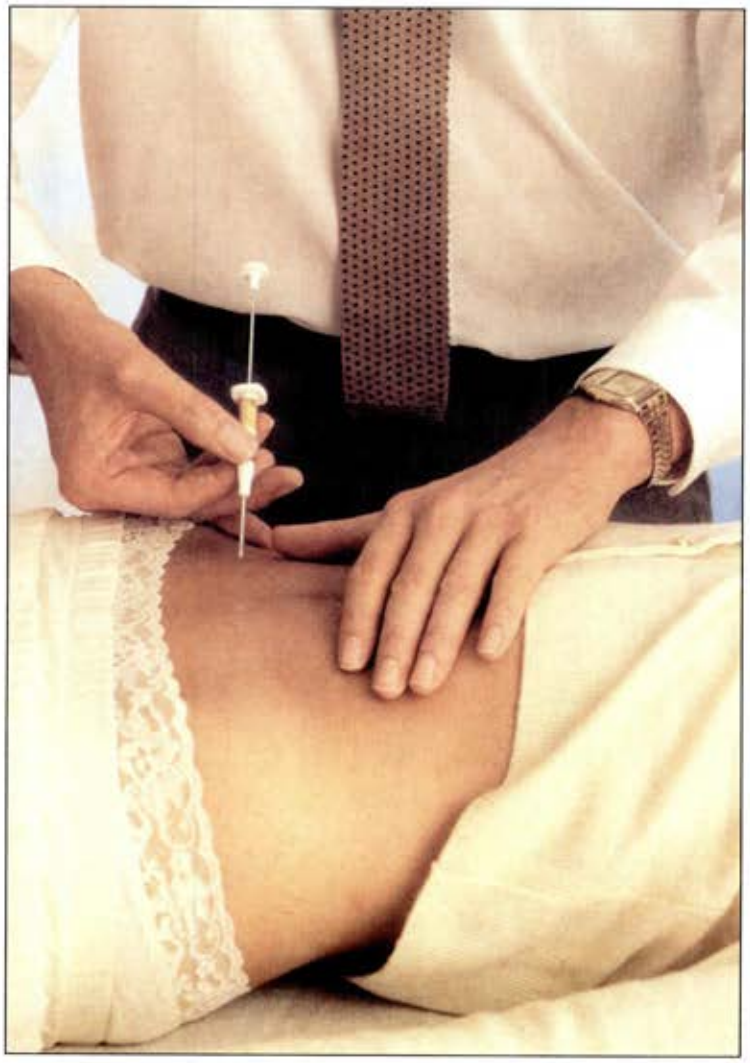

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DAGANATOS BETEGEK FÁJDALOMCSILLAPÍTÁSÁNAK ÚJABB LEHETŐSÉGEI

Az Egészségügyi Világszervezet Nemzetközi Fájdalomcsillapító Társaság (IASP) szakértői az elmúlt évtizedben jól alkalmazható módszertani ajánlást dolgoztak ki, amely elsősorban megfelelő gyógyszer-kombinációk előírásán alapul. A WHO ajánlás alkalmazásával, csak gyógyszerekkel a daganatos fájdalom kb. 70-80%-ban kielégítően enyhíthető. A gyógyszeres kezelés szükség esetén kiegészíthető egyéb eljárásokkal, mint pl. non-invazív fájdalomcsillapító eljárások, ideg-blokádok, idegsebészeti beavatkozások. A non-invazív eljárások közül a daganatos fájdalomcsillapításra leggyakrabban a TENS-t (transcutan elektromos idegstimuláció) használják, főleg a másodlagos myalgia, illetve a neuropathiás fájdalmak enyhítésére.

Az utóbbi években egy új opioid non-invazív eljárást mutattak be, a **fentanyl** transdermalis rendszert (**fentanyl TTS**). A **fentanyl**, egy opioid fájdalomcsillapító szer, amelyik elsősorban az úgynevezett m-opioid receptorokra hat. Elsődleges gyógyhatása a fájdalomcsillapítás és a nyugtatás. A **fentanyl** minimális fájdalomcsillapító szérum koncentrációja az opioid-naív betegekben 0.3 és 1.5 ng/ml között van.

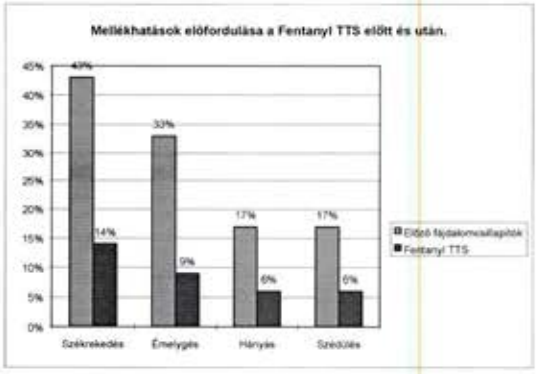
A **fentanyl TTS** négy különböző kiszerelési formában kerül forgalomba: 10, 20, 30 és 40 cm^2 alapterületű tapaszok, amelyek biztosítják, hogy a bőrön keresztül óránként 25, 50, 75 és 100 mg fentanyl jut a vérkeringésbe. Ez 0.6, 1.2, 1.8 és 2.4 mg **fentanyl** napi adagnak felel meg.

A **TTS** biztosítja a **fentanyl** folyamatos bejuttatását. A folyamatos **fentanyl** bejuttatást a rendszerből egy polimerizált membrán szabályozza. Az első tapasz felhelyezése után a szérum **fentanyl** koncentráció fokozatosan emelkedik, általában 12-24 óra múlva éri el a megfelelő szintet, ezt követően változatlan marad 72 órán keresztül.

A **fentanyl TTS** dózisát a beteg állapotától függően minden esetben egyénileg kell meghatározni. Az 1. táblázat mutatja az ajánlott **fentanyl TTS** dózist a napi orális morfin igény alapján.

1. Táblázat A szájon keresztül felvett, 24 órás morfin mennyiségnek megfelelő fentanyl TTS mennyiség

24-órás orális morfin adag (mg/nap)	Fentanyl TTS adag (mg/h)
<135	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300



A klinikai kipróbálások során bebizonyosodott, hogy a **fentanyl TTS** rendkívül hatékony a krónikus fájdalmak csillapítására. A fájdalom skálán végzett felmérések kimutatták, hogy a betegek fájdalom pont értékei a **fentanyl TTS** kezelés során az előző opioid kezeléshez viszonyítva szignifikánsan alacsonyabbak voltak. A tartós fájdalomcsillapítás **fentanyl TTS** adásával akár 2 éven keresztül is fenntartható. Ez a kiszerelési forma a betegek számára is nagyon előnyös, mivel a tapaszokat csak 3 naponként kell cserélni. Mellékhatások más opoid készítményekhez viszonyítva ritkábban fordulnak elő *(1. Ábra)*.

A **fentanyl TTS** egyedülálló fájdalomcsillapító, amelyet először az Egyesült Államokban vezettek be 1990-ben. Egy évvel később Kanadában került forgalomba. Jelenleg Nagy Britanniában, Svédországban, Dél Koreában, Hollandiában és Németországban is sikeresen használják. Magyarországon már törzskönyvezték, és várhatóan 1997-ben kerül forgalomba.

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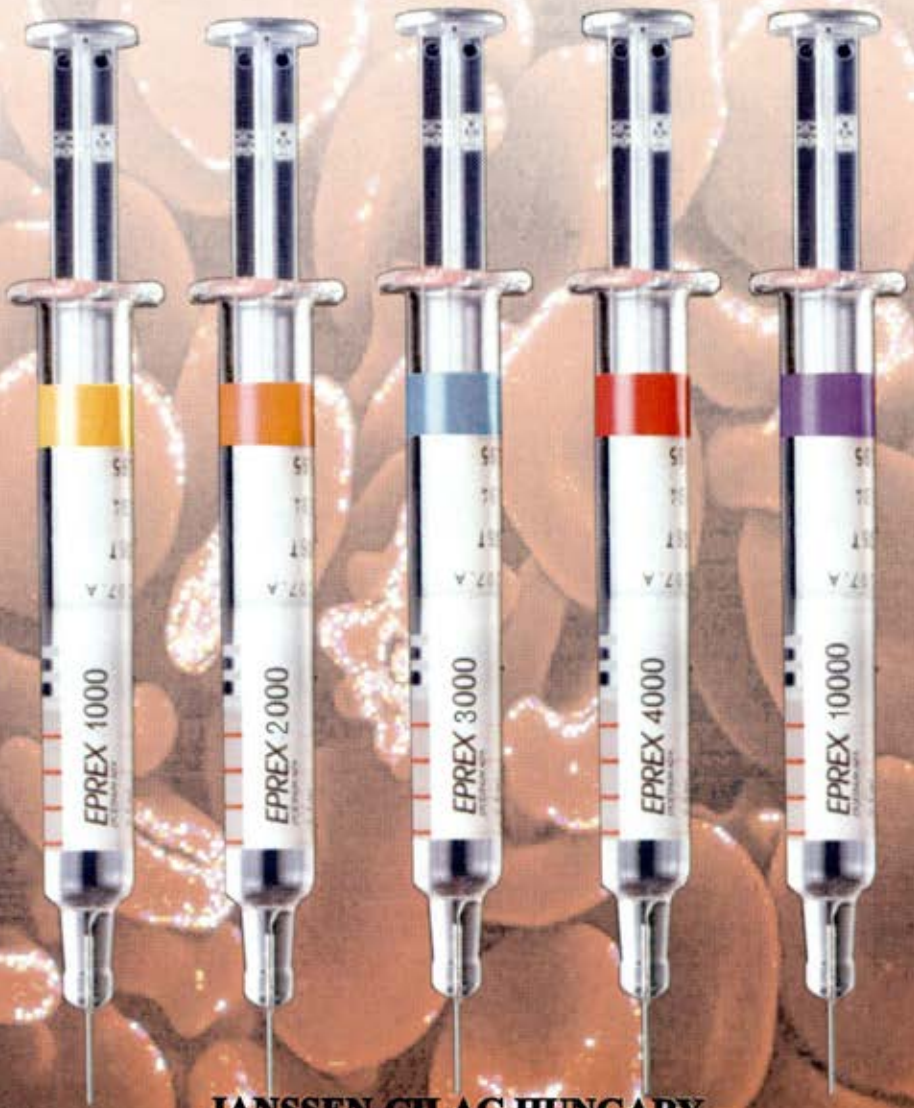

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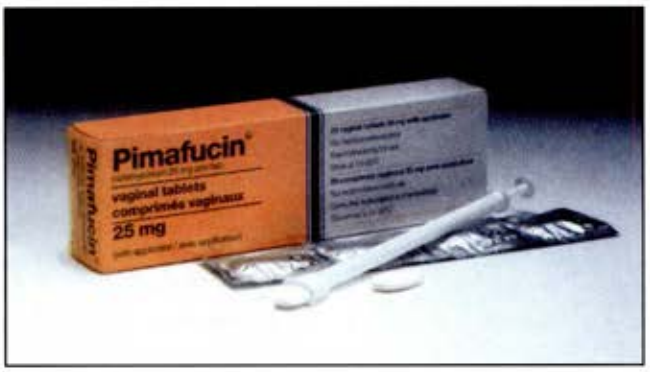

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CHIRON

The role of radiation therapy in the management of invasive squamous cell carcinoma of the vulva

PÉTER BŐSZE, M.D.

Department of Gynecologic Oncology, Saint Stephan Hospital, Budapest

INTRODUCTION Radical vulvectomy with bilateral groin lymphadenectomy has been regarded as standard treatment for resectable invasive squamous vulvar carcinoma. There is no advantage in routinely performing pelvic node dissection (1). Current management of pelvic lymph nodes is guided by prognostic factors and includes dissection of any enlarged nodes followed by postoperative groin and pelvic radiotherapy. The place of pelvic lymphadenectomy in high-risk patients of developing pelvic recurrences has yet to be determined. En bloc radical vulvectomy and bilateral inguinofemoral node dissection has been superseded by the triple incision technique (radical vulvectomy with separate groin incisions) (2), practically in all patients with primary tumor confined to the vulva who do not have enlarged groin nodes. The triple incision technique has been demonstrated to be as effective as the en bloc procedure and has been associate with significantly less morbidity (3). For small primary tumor first modified radical vulvectomy, later radical local excision has been advocated with comparable local control and survival rates. In fact, the surgical margins adjacent to the tumor are the same with radical vulvectomy and radical local excision.

Some of the problems associated with the basic surgical strategy include:

- Radical vulvectomy is a mutilating procedure which is not infrequently associated with devastating psychosocial consequences and compromised sexual function in younger women.
- Mild to severe complications frequently occur, some of them, especially leg edema following groin node dissection are severely debilitating.
- Women with vulvar cancer are at high surgical risk due to advanced age and associated medical conditions such as obesity, hypertension, diabetes, cardiovascular diseases, etc.

Over the past 20 years, great strides have been made to overcome some of the major concerns associated with the traditional management of invasive squamous carcinoma of the vulva. These include less radical surgical excision of the primary tumor in early cases, replacing exenterative treatment with organ-sparing procedures in advanced stages, recognition the need of individualized treatment, confirm the validity of the sentinel node concept, introduction of a safe a simple method of intraoperative lymphatic mapping (4), etc. This later approach is a potentially valuable intraoperative tool for assuring removal of the sentinel node and thereby increasing the efficacy and defining the extent of groin dissection and whereby reducing the incidence of lymphedeme.

In the past, the role of irradiation in the primary treatment of vulvar cancer was limited, mainly, because the results were less favorable than those with surgery, and perhaps, because of the high incidence of severe complications and poor tolerance of radiation therapy by the vulvar tissue. However, several recent reports suggest that with high-energy equipment, radiation therapy can be performed without producing radiation necrosis and significant severe complications. The advantages of radiotherapy in the management of squamous cell carcinoma of the vulva have been increasingly appreciated and the indications for are evolving. The possible sites of irradiation include 1. vulva with the adjacent tissue/organs, 2. groin lymph nodes and 3. pelvic lymph nodes.

RADIOSENSITIVITY OF SQUAMOUS CELL CARCINOMA OF THE VULVA

Sufficient data have accumulated suggesting that irradiation could eradicate or at least cause major regression of vulvar cancer in a significant proportion of patients (5-10). Like squamous carcinomas of the anal canal, vulvar cancer appears to regress rapidly during radiation therapy. Complete remission may occur before the treatment is completed but, as a rule, within 4 to 6 weeks of completion of irradiation. Thus, vulvar cancer is radiosensitive; probably as sensitive as squamous cancer of the skin and more sensitive than that of the cervix or vagina. However, necrotic tumors and atrophic epithelial structures often fail to respond satisfactorily to radiation therapy (8).

CAN RADIATION THERAPY ERADICATE INGUINAL LYMPH NODE METASTASES? Clinical evidence suggests that microscopic groin

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node metastases may adequately be treated with radiation therapy (7, 11-15). However, macroscopic inguinal node metastasis usually requires surgical excision prior to irradiation. Grossly positive nodes are unlikely to be cured by irradiation alone (11, 16).

RADICAL VULVECTOMY WITH ELECTIVE INGUINAL RADIATION

Elective groin radiation, i.e. radiation therapy to the groin without inguinofemoral lymphadenectomy combined with the surgical management of the primary tumor has been advocated. Elective groin node irradiation may be given simultaneously or after the surgical treatment of the primary tumor. The largest series of 607 patients with various stages of vulvar cancer treated with elective groin radiation has been reported on from Vienna (17-18). Nodes larger than 2 cm were excised. The cure rate was comparable with that of groin node dissection irrespective of the clinical nodal status. In this series the pelvic nodes were not irradiated. *Schultz et al.* (19) reported a single regional failure of 38 patients with elective groin radiation versus 5 regional failures out of 35 nonirradiated patients. *Henderson et al.* (20) studied 41 patients (31 St I, 6 St II, 4 St III) with no palpable nodes treated with elective groin radiotherapy. Only one patient experienced regional recurrence that was outside the irradiated area. The advantages of elective ilioinguinal node irradiation have also been demonstrated in other series (12, 17, 21-23). Recently, the GOG (24) reported the results of a phase III study. Patients with invasive vulvar cancer with no clinically suspect groin nodes were allocated to either undergo inguinofemoral node dissection followed by postoperative groin radiation for patients with positive nodes or receive primary groin irradiation of 50 Gy to a depth of 3 cm below the skin surface. Enlarged nodes were cytologically evaluated and those with positive findings were excluded. The study was closed prematurely because of the high incidence of groin recurrences in the elective radiation arm of the study. This finding is against to give primary groin radiation. However, this study has been criticized (25). The failure in the radiation arm might be attributable to methodological error because the deepest groin nodes measured on CT scans were to be located deeper than 3 cm (around 5 cm) below the skin surface in approximately half of the patients, consequently they did not receive adequate radiation dose. This criticism along with the experience accumulated in the literature suggests that elective groin radiation is an alternative to full inguinofemoral lymphadenectomy (26). Lower incidence of acute and delayed morbidity including leg edema after elective groin radiotherapy has been reported, and this is the major advantage of this approach as compared to the traditional surgical management of the groin nodes with or without postoperative groin radiation.

PREOPERATIVE RADIATION OF THE PRIMARY TUMOR

EARLY STAGES Currently, we do not have reports suggesting that preoperative radiation of T1 or T2 tumors is beneficial unless the tumor is located on either the perineum or clitoris. Surgery alone is probably an adequate treatment for such lesions. Stage I and II squamous cell carcinoma of the vulva encroaches on either the perineum or clitoris may well be treated with preoperative irradiation or chemoradiotherapy to reduce tumor size and thereby permitting tissue sparing surgical excision.

LOCALLY ADVANCED LESIONS Locally advanced vulvar cancer has a varied presentation and may be defined as tumors involving the lower urethra, vagina, anus (T3 primary tumor) or bladder mucosa, rectal mucosa, upper urethra, pelvic bone (T4 primary tumor). *Hoffman et al.* (27) consider vulvar cancer to be locally advanced when the tumor cannot be locally managed by a radical vulvar resection.

Primary surgical management of locally advanced vulvar cancer with the aim of adequate surgical clearance requires radical, mostly exenterative intervention with additional groin node with or without pelvic node dissection. This may include resection of the pubic bone in selected cases (28). *Radical vulvectomy* for T3 tumors has been reported to carry a high risk of local recurrence (29). Depending on the tumor location, with *anovulvectomy* or *radical vulvectomy and partial resection of the rectum with reconstruction or, even preservation of the anal sphincter* the primary locally advanced tumor can adequately be managed (30-31) *Pelvic exenteration* (anterior, posterior or total), as primary therapy, is rarely indicated. It is a viable option when organ-preserving treatment, i.e., preoperative radiation with or without chemotherapy has failed. It may also be indicated for large invasive primary vulvar cancer in patient not eligible for organ preservation (32). The major prognostic factor in terms of recurrence following pelvic exenteration is the presence of lymph node metastases (27, 33-34). Thus, careful regional node dissection prior to exenteration is required. Locally advanced disease with node involvement apparently cannot be controlled by pelvic exenteration alone. In the absence of nodal involvement, 50-75% 5-year survival rate can be expected (32-34). Therefore, according to *Homesley et al.* (35) it is not reasonable to utilize exenterative surgery in patients with locally advanced primary carcinoma of the vulva who have more than one or perhaps two microscopic positive inguino-femoral nodes. Other prognostic factors for survival include tumor size and clear margins. Ultraradical surgical approaches are mutilating often with compromised organ function, psychologic morbidity and significant risk of medical complications (36-37). Age per se is not a contraindication, pelvic exenteration can safely performed in elderly women (32, 38).

Preoperative irradiation (external, interstitial) with or without chemotherapy has been utilized to bring about tumor shrinkage, thus permitting less radical surgery with possible sparing bladder and/or rectal function (16, 39-43). It has been assumed and was one of the reasons to administer radiation therapy prior to surgery, that preoperative external radiation would control any microscopic disease in the uninvolved vulva to allow conservative surgical excision. However, there is no evidence that the normal-looking vulva harbors microscopic tumor deposits.

Boronow (40) was the first to suggest preoperative irradiation with intracavitary radium with or without external beam irradiation in women with locally advanced vulvar cancer to eliminate internal tumor followed by surgical excision of the external genital disease. Subsequently, *Hacker et al.* (16) reported on 8 patients treated with teletherapy and there was no residual disease in the specimens of 4 patients. Long-term survival has been achieved in two patients with tumors fixed to the pelvic bones. With further experience external beam irradiation with use of brachytherapy in selected cases only has been recommended. Although most reported series have been based on small numbers, tumor regression following 40-50 Gy external beam irradiation apparently is not infrequent with complete response in half of the patients depending on, the stage, the size of the tumor and the radiation dose delivered (16, 41, 44). Exenterative surgery or removal of the entire vulva was not necessary in patients with complete or nearly complete disappearance of all gross disease. The prognosis of complete responders as compared to partial responder is significantly better. The outcome of non-responders is generally poor. The width of the tumor-free resection margins appears to be important in terms of local control. Subclinical residual disease has been found in the surgical specimen in a substantial number of patients with complete disappearance of all gross tumor following radiation therapy, and excision of the tumor bed has been advocated. The overall results of combined treatment of locally advanced disease show that the cure rate is comparable or even better than that of radical surgery, and the primary mortality and treatment morbidity are significantly decreased. Bladder and/or rectal function may be preserved in approximately 70% of patients with T3 or T4 lesions. Sparing of vulvar tissue may also be possible in some instances.

THE ROLE OF POSTOPERATIVE VULVAR AND GROIN RADIATION THERAPY

POSTOPERATIVE IRRADIATION OF THE VULVA No prospective randomized study has been reported on the value of adjunctive vulvar radiation therapy after radical vulvectomy. Some reports suggest that radiation treatment may have value in controlling vulvar lesion (45). Whether it is true for patients with properly excised vulvar tumor has yet to be determined. At present, surgery alone is the preferred treatment in such cases. Local vulvar recurrence is not uncommon when the surgical margin of the excised vulvar tumor is not adequate, and therefore postoperative vulvar radiation appears to be indicated in this setting. However, surgical margin as a prognostic factor has not been subjected in most studies. Consequently, the beneficial effect of the adjuvant vulvar radiation therapy is not clear.

POSTOPERATIVE GROIN NODE IRRADIATION There has been uncertainty regarding the indications for postoperative groin irradiation. Patients with histologically negative groin nodes or those with one small unilateral groin metastasis are at very low-risk of developing regional, pelvic or distant recurrences. Thus, adjuvant radiation therapy is probably of no therapeutic value (35). However, in view of the high incidence of regional, pelvic and distant failures in patients with large and/or two or more small groin metastases, postoperative groin irradiation with or without concurrent chemotherapy appears to be justified. Lymphadenectomy alone is probably not curative in patients with fixed or ulcerated groin node metastases (bulky N2 or N3 groin nodes), whereas groin lymphadenectomy and postoperative groin irradiation has been shown to decrease regional recurrence and improve survival (11, 16, 35, 46). *Hacker* (47) does not advocate full inguinofemoral lymphadenectomy in addition to the dissection all the enlarged nodes in the presence of bulky positive groin node(s) prior to radiation to avoid severe leg edema. Recent studies (48-49) show that not only the number of the positive nodes as well as whether they are microscopic or bulky, but the size of the small and the anatomic structure of the lymph node metastases have prognostic significance. The 5-year survival of metastatic groin nodes <5 mm, 5-15 mm and >15 mm were 91%, 42% and 21%, respectively (48). A significant difference in survival has also been reported according to the presence or absence of extracapsulal involvement of the metastatic nodes; patients with extracapsulal spread did significantly worse (48-49). The prognosis seemed to be related to the size within the lymphatic secondary with a significantly decreased survival when >50% of the node was occupied by the tumor cells in patients with one positive groin node (49).

THE ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF PELVIC LYMPH NODES Most reports (13, 50-53) strongly suggest that pelvic node metastases are rare in the absence of positive groin nodes regardless of the location of the primary tumor, and patients with one or no microscopically positive groin node do not require any further therapy including treatment of the pelvic lymph nodes. In the UCLA series (54) no positive pelvic node was encountered in patients with two or less unilateral groin nodes. Location of the pelvic nodal metastasis has been reported to be invariably on the same side as the positive groin nodes (50, 54-56). Unfortunately, none of the imaging techniques are reliable in evaluating pelvic lymph node metastases, although enlarged pelvic nodes are readily picked up by CT or abdominal ultrasound scanning. Microscopic nodal involvement might be diagnosed using pelvic lymphangiography. *Hacker et al.* (54) reported no positive pelvic nodes in patients without clinically suspicious or evident groin lymph nodes. Thus, careful preoperative assessment of the inguinofemoral nodes is one of the most accurate predictors of metastasis to pelvic nodes. Other reports (35), however, did not confirm this finding.

Extension of the radiation field to the pelvic nodes is probably associated with increased treatment morbidity. In the past, primary pelvic radiation combined with elective groin radiotherapy has been proposed irrespective of the groin nodal status. Currently, there is no evidence to substantiate this approach (18). Treatment of the pelvic nodes seem to be indicated only in patients with enlarged and/or two or more microscopi-

cally positive groin nodes. This should be ipsilateral in the presence of unilateral groin node involvement. Radiotherapy to the pelvic nodes is administered in combination with groin irradiation following wound healing, in general, within six weeks postoperatively.

PELVIC LYMPHADENECTOMY VERSUS POSTOPERATIVE PELVIC RADIATION As pointed out above, routine pelvic lymphadenectomy has no place in the management of squamous cell carcinoma of the vulva (1). It may be an alternative to postoperative pelvic irradiation in high-risk patients. The literature data on the efficacy of postoperative pelvic irradiation combined with inguinofemoral radiation treatment in patients at high-risk, i.e. with grossly positive and/or two or more small positive groin nodes are controversial. The Gynecology Oncology Group studied 114 patients with vulvar cancer and histologically proven positive groin nodes who were randomized to either radiation therapy to the groin and pelvis or pelvic node dissection. In this prospective study the relative two-year survival was superior for the group of patients receiving radiation therapy. The major survival advantage for radiation therapy was in patients with either clinical N2 and N3 or two or more microscopic positive groin nodes. Adjuvant radiation was more effective in reducing the incidence of groin recurrences. The beneficial effect of pelvic irradiation was not evident, in fact, less recurrence occurred in the lymphadenectomy arm. *Kucera and Weghaupt* (18) do not recommend elective pelvic node radiation because of the poor general condition and advanced age of the patients. Other investigators (19, 40, 57), however, are in favor of radiating the whole pelvis or the pelvic nodes in addition to groin node radiation therapy. *Boronow et al.* (58) did not report on pelvic recurrences after pelvic irradiation as integrated part of combined surgical and radiation therapy. In view of *Hacker* (47), radiation therapy is unlikely to sterilize enlarged pelvic nodes. He recommends to remove any enlarged pelvic nodes without full pelvic node dissection via separate incision prior radiation therapy.

At present, the therapeutic value of postoperative pelvic node radiation in vulvar cancer remains unknown. Considering pelvic node radiation one should keep in mind that pelvic lymphadenectomy adds nothing to the cure of patients with histologically negative pelvic nodes and it is of little value in patients with pelvic node metastasis (35). In addition, this procedure may be associated with a slight increase in operative morbidity and occasional mortality.

RADIATION THERAPY ALONE Apparently, there is no place for curative radiotherapy alone in the management of *early carcinoma of the vulva* unless the patient is unfit for surgery. However, this is very uncommon. In the authors series, in accordance with the literature data, wide local excision of the primary could be accomplished even in patients with severe medical problems.

Although there is a dearth of information, the results of radiation therapy alone in *advanced carcinoma of the vulva* have been discouraging and are inferior to those of combining radiation with conservative surgery (59). With radical radiotherapy alone approximately 40% local control rate can be expected (6, 60). Complete response to radiation therapy does not result in local control in all instances. As mentioned above, residual disease is not infrequent in the tumor site, thus, removal of the tumor bed has been advocated. Local excision of the residual tumor or tumor bed, in general, is a simple procedure, which can be carried out even in frail patients. *Thomas et al.* (61) suggest irradiation with or without chemotherapy as definitive management for those with midline vulvar lesions such as clitoral, vaginal and anal lesions where surgical removal is accompanied by major cosmetic and functional morbidity. In the authors' view this approach deserves further studies before one can embark on that strategy. For patients with large vulvar cancer radiation treatment alone is rarely curative.

In contrast to microscopic *nodal involvement*, clinical N2 and N_3 groin nodes can rarely be treated effectively with radiation alone. *Backström et al.* (11) reported on one patient with N3 groin node cured by radiation alone. Surgical excision of N2 or N3 groin nodes, in conjunction with radiation, has been recommended. *Henderson et al.* (20) do not advocate treatment of clinically positive groin nodes by irradiation alone since the high-dose that required will produce fibrosis in a substantial number of patients. In the absence of clinically enlarged node, groin node dissection has not been recommended to reduce the incidence of lymphedema associated with inguinofemoral lymphadenectomy and radiotherapy.

Radiation therapy alone may be used effectively as a palliative measure to relieve symptoms. Even cure has been reported on in this group of patients (41).

CHEMORADIOTHERAPY OF PRIMARY VULVAR CANCER The most frequently used agents in squamous cell vulvar cancer are cisplatin, 5-fluorouracil, mitomycin-C and bleomycin. Exclusive chemotherapy in vulvar carcinoma has failed to show any significant advantage (62). These agents, however, have been demonstrated in vitro and in clinical trials to increase the sensitivity of the squamous cancer cell of the vulva to radiation therapy (63). Recent evidence suggests that paclitaxel increases the sensitivity of vulvar carcinoma cell lines to radiation in vitro (64).

EARLY STAGES As with radiation, chemoradiotherapy has no established place in the management of early stage squamous cell carcinoma of the vulva. This may be beneficial in patients with midline tumors to permit more adequate local excision and organ sparing. *Lupi et al.* (65) believe that in pathologic complete responders surgery may be spared.

LOCALLY ADVANCED LESIONS Following the pioneer report by *Nigro et al.* (66) on the encouraging experience in treating

squamous cell anal carcinoma with preoperative chemoradiation therapy, high response rate to chemoradiotherapy in locally advanced carcinoma of the vulva has been reported (61, 67-71). *Whitaker et al.* (72) reported a pilot study of chemoradiotherapy in advanced carcinoma of the vulva. This study has recently been updated (73). Thirty-seven patients with advanced tumor (19 primary and 16 recurrent), that would have necessitated exenterative surgery were treated with chemoradiotherapy (mitomycin-C and 5-FU) and with surgery reserved as salvage treatment at 3 months after completion of treatment in those failing to enter complete remission. The local control rate was high in complete responders although the follow-up might not be long enough to draw final conclusions. The outcome for those patients failing to obtain complete response was disappointing. Whether it is due to the 3-month interval before performing surgery has jet to be determined. More probably, it is attributable to the biological behavior of the tumor. In general, surgery is carried out 4 to 6 weeks following radiation or chemoradiotherapy in order to allow healing of the local reactions and further regression of the tumor. *Berek et al.* (74) reported 83% 3-year survival rate in 12 patients with advanced disease treated with preoperative chemoradiotherapy (Cisplatin + 5-FU). *Thomas et al.* (61) using mitomycin-C, 5-FU and continuous radiotherapy reported on 6 clinically complete response of 9 patients with advanced disease. Three of them subsequently experienced local recurrence. Local recurrence may occur in pathologically complete responders diagnosed by multiple biopsy of the tumor side. These findings are in favor of excision of the tumor bed following complete disappearance of the primary tumor. *Sebag-Montefiore et al.* (73) has challenged this concept and believe that the high local control rate of the primary and recurrent disease in pathologically complete responders might not justify excision of the tumor bed, thus, sparing patients from surgery altogether. *Lupi et al.* (65) reported 31 patients with T3-T4N2 primary (24 cases) or recurrent (7 cases) vulvar cancer treated with concurrent chemoradiotherapy (mitomycin-C + 5-FU and pelvic radiation) followed by radical surgery. They achieved 42% clinical complete remission (pCR was 36%). It is noteworthy the chemoradiation was effective in eradicating regional and pelvic lymph node metastasis in a substantial number of patients. The actuarial 5-year survival rate was 55%. The toxicity and operative morbidity and mortality were acceptable in all but those patients with recurrent disease. *Russell et al.* (75) reported on 80% clinical complete response in 25 women with advanced disease. Treatment with the combination of bleomycin and radiation has resulted in unsatisfactory outcome (76).

In conclusion, chemoradiotherapy is safe but not without toxicity. The overall response rate is high (>90%) with complete response rates of 40-80%. Combining chemoradiation with surgery approximately 80% local control can be achieved, avoiding exenterative procedures in almost all instances. Chemoradiotherapy is effective in treating positive lymph nodes. Whether these can be translated into long-term survival benefit is not clear.

RECURRENT DISEASE Vulvar recurrences can be treated with some effectiveness using radiation therapy (11, 41-42). For small vulvar recurrences (T1 or T2 recurrent tumor) wide surgical excision with or without adjunctive treatment has been advocated (77). Wide local excision alone has been reported to be successful for isolated skin bride recurrences as well provided surgical margins are adequate (78-79). Inadequate margins require adjunctive radiation therapy (80). Prognostic factors adversely associated with survival include early (<1-2 years) recurrences, positive groin nodes at the time of primary surgery and recurrences outside of the primary location of the vulva (81-82). Local excision of large vulvar recurrence (>5 cm) has been commonly associated with local failure. Adjuvant radiotherapy and or chemotherapy has been used. The outcome for patients with recurrence outside the primary vulvar site is poor irrespective whether it is treated with surgery alone or with combined approaches. For patients with tumors extending to the urethral or perennial area primary radiation therapy has been recommended, which may be followed by local resection of the tumor bed 4 to 6 weeks after irradiation. The residual tumor should be locally excised in an attempt to cure the patients. As with locally advanced primary tumor, some locally advanced recurrent disease, although rarely, may require exenterative surgical procedure. Again the major prognostic factor in terms of disease control is the nodal involvement (27, 32).

Re-irradiation of a recurrent vulvar lesion may also be effective in a small subset of patients. The longer the disease free interval prior to the development of recurrent tumor the better the results of re-irradiation.

Chemotherapy is ineffective in local recurrence previously treated with radiation therapy with or without concurrent chemotherapy. Chemoradiotherapy has been reported to have a place in the management of local recurrence following vulvectomy or wide local excision (73). There has been increasing evidence to show that with chemoradiotherapy with or without surgery local-regional control can be achieved in a high proportion of recurrent disease (65, 73).

The curative value of *radiation therapy* for nodal relapse is limited because both local and distant failure is common in this group. To improve local control of the recurrent groin disease surgical excision of the enlarged node(s) should be performed if feasible. In spite of this, the prognosis has been uniformly poor. Thus primary control of the vulvar cancer and the regional nodes is of paramount importance. Recent reports on *chemoradiotherapy* seem to suggest the efficacy of this approach in eradicating both groin and pelvic node metastasis in patients with recurrent disease

TECHNIQUE AND DOSAGE OF IRRADIATION

PRIMARY TUMOR External beam therapy seems to be probably more effective than brachytherapy or implants and carries less risk for side effects. The energy of irradiation is crucial. Only

high-energy photons from supervoltage machines (16, 44) and, perhaps high-energy electron irradiation (6) appear to be adequate for radiation treatment for vulvar cancer. Brachytherapy as a sole modality may be effective in controlling small volume disease only. Combination of local irradiation with external irradiation does not seem to improve treatment results unless the proximal half of the vagina is involved because vaginal carcinoma does seem to be as radiosensitive as vulvar cancer (16). Nevertheless, intracavitary irradiation or implants can be used as a boost to external therapy.

Hacker et al. (16) recommended that external radiation to the primary tumor should be delivered through parallel opposed (AP) anterior and posterior (PA) pelvic portals, with both fields being treated daily in an isocentric fashion. This will deliver a relatively homogeneous dose of irradiation to the vulva, vagina and rectovaginal septum but not to the pelvic lymph nodes. Should the groin and pelvic nodes be encompassed in the irradiation field the AP and PA portals can be enlarged. Others (10, 41) are in favor of using perennial portals. Frog leg position of the patient also has support (59).

The recommended dosage for small tumors is usually 50 Gy, with daily fraction size of 1.8 Gy or less. *Thomas et al.* (83) reported minimal late sequelae in patients treated with 1.75 Gy or less daily fractions. *Pao et al.* (59) found no dose response for subclinical disease between 45 and 75 Gy. To achieve complete regression of large primary tumors higher doses (up to 85 Gy) should be administered (15).

LYMPH NODES A variety of techniques has been used to give inguinal lymph node irradiation. *Henderson et al.* (20) recommended the method of two separate anterior shaped fields. *Simonsen et al.* (84) are in favor of using a single field technique.

The fields of radiation should encompass the superficial and deep inguinal-femoral nodes with an appropriate safety margin, perhaps extending to the margin of the vulvar excision. Whole pelvis radiation therapy may be administered to treat both groins and obturator, external and internal iliac areas, via either 4-field box technique or AP and PA opposed fields.

The most commonly used tumor dose at 2 to 3 cm depth is 45 to 50 Gy in five weeks, with 1.8-2 Gy per fraction (12, 18-19). According to *Henderson et al.* (20) the minimum lymph node dose should not be less than 50 Gy. *Simonsen et al.* (84) recommended higher dose in patients with perinodular growth. Patients with grossly positive nodes require a higher dose unless the enlarged nodes are dissected. Should regional postoperative radiotherapy is indicated, the routine use of midline block has not advocated (85).

The energy of radiation depends on the amount of the overlying subcutaneous tissue. Very high energy irradiation may underdose superficial lymph nodes that lie immediately under the skin, e.g. in thin patients. Although most authors have utilized telecobalt, telecesium or x-ray therapy there seems to be an advantage of combining photon therapy with electron radiation. However, the use of electrons for the entire treatment has not been recommended because moderate to severe skin and subcutaneous changes will occur with high-energy electrons (20).

COMPLICATIONS OF RADIATION THERAPY

RADIATION OF THE VULVA Orthovoltage treatment of the primary tumor has been associated with severe complications, mostly necrosis (17, 86). The use of electron irradiation alone to treat vulvar cancer carries a relatively high risk of severe complications (6). With the advent of megavoltage machines, newer technology in radiation planning and delivery, severe complications such as *vulvar fibrosis and necrosis* are uncommon. Their appearance is related to the daily fraction dose and total dose of radiation. In contrast, *moist desquamation* of the skin is not infrequent and usually appears after the vulva has received a dose of 30 to 45 Gy, necessitating a short treatment interruption (16, 61). Considerable skill is required from trained nurses to manage this complication. Other mild adverse effects include *erythema, atrophy* and *telangiectasis. Thrombo-embolic disease, fistula formation* and *stenosis of the introitus* are rare. *Myelosuppresion* is also infrequent and usually mild.

GROIN IRRADIATION Acute side effects of inguinal irradiation have been limited to dry and occasionally small patches of moist *desquamation of the skin. Inguinal fibrosis* is dose dependent and usually mild to moderate and asymptomatic in most cases. This side effect is uncommon if the dose is less than 50 Gy. Patients with a marked amount of subcutaneous fat are particularly apt to develop fibrosis (20). The risk of *lymphedema* is extremely low with most series of no such complications. A *vascular necrosis* of the thigh with or without femoral neck fracture is a major worry which has been reported to occur at doses as low as 26 Gy to the femoral head. The cumulative actuarial incidence of femoral neck fracture following groin irradiation was 11% at 5 years and 15% at 10 years and was related to dose, cigarette use and x-ray evidence of osteoporosis prior to radiotherapy (87). This sequel seems to inevitably occur in some patients treated with pelvic irradiation. Nevertheless, care should be taken to minimize the dose to the femoral base where possible, e.g. by shielding the femoral neck, without compromising treatment results. This may be achieved by delivering a portion of the inguinal lymph node treatment with electrons (20, 87). Major *bowel complication* has been reported on in a few patients treated with pelvic irradiation (41) or with chemoradiotherapy (73).

Combination of surgical and radiation treatment of the groin nodes does not seem to increase the complication rate (22, 35). In contrast, *Hacker* (47) reported severe leg edema after full inguinofemoral node dissection combined with groin irradiation. Wound healing is probably not altered by pre- or postoperative irradiation.

Close evaluation of the patients throughout and following irradiation as well as optimal skin care including taping the skin fields apart, keeping intact skin dry without using ointment, and perennial hygiene are important to avoid side effects and decrease the need for interruption of treatment. Counseling prior to radiation to improve the tolerance of radiation is also important for vulvar skin reaction which is probably inevitable. Moist desquamation responds well to local antiseptics and topical cortico-steroids.

CONCLUSIONS The role of radiation therapy in the management of vulvar cancer has not been adequately explored. The evidence available suggests that irradiation in combining with surgery may improve treatment results and quality of life.

The management of patients presenting with early stage disease has been surgical with satisfactory outcome in terms of local control and long term survival. There is no place for radiotherapy in small stage I and II squamous cell carcinoma of the vulva unless the tumor is located on the perineum or clitoris. T1 and T2 lesions encroaches on either the perineum or clitoris may well be treated with preoperative irradiation or chemoradiotherapy to bring about tumor shrinkage and thereby permitting tissue sparing surgical excision.

Elective groin irradiation replacing inguinofemoral lymph node dissection combined with surgical excision of the primary tumor has not been practiced in routine setting.

As stated by *Neville Hacker* (47): "with the experience now accrued, preoperative radiation, with or without concurrent chemotherapy, should be regarded as the treatment of first choice for patients with advanced vulvar cancer who would otherwise require some type of pelvic exenteration." Pelvic exenteration is rarely indicated. It is a viable option when organ-preserving treatment, i.e., preoperative radiation with or without chemotherapy has failed. The combined approach as opposed to exenterative surgery is significantly superior in terms of survival in patients with positive groin nodes. Whether the tumor bed should be excised in those patients with locally advanced primary tumor who obtain complete remission following radiation or chemoradiotherapy is not clear and requires further studies. The author is in favor of excising the tumor bed.

Most patients with isolated small vulvar recurrence can be saved with further surgical excision. More advanced local recurrent tumor, however, require radiation or chemoradiotherapy to avoid exenterative procedure. Residual tumors in those without pathologic complete remission and perhaps, the tumor bed in complete responders should be excised. Further studies are needed to determine the long-term outcome of radiation therapy alone or chemoradiotherapy without subsequent excision of the tumor site in those with pathologic complete response.

Radiation therapy is commonly associated with toxicity including both acute and late complications, the latter being more severe. The major acute toxicity is the development of perennial moist desquamation, often resulting in treatment delay. With the advent of megavoltage machines, newer technology in radiation planning and delivery, severe complications such as vulvar fibrosis and necrosis are uncommon.

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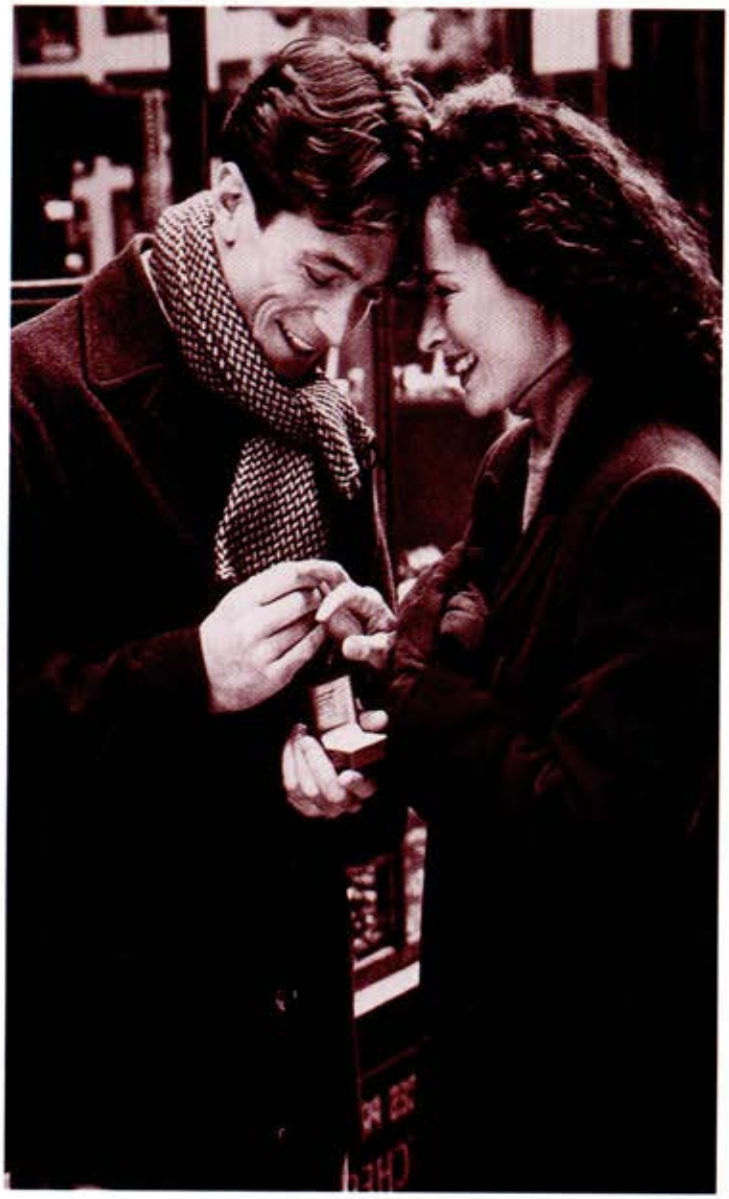

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- ❖ megrövidült ciklus,
- ❖ gyenge havi vérzés,
- ❖ hiperandrogén kórképek (hirzutizmus, akne, androgén típusú hajhullás, seborrhoea)
- ❖ méh- és/vagy emlőfejletlenség,
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- ❖ pecsételő nyomvérzés,
- ❖ vérzéskimaradás, hypomenorrhoea,
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- ❖ szubdepresszív hangulati ingadozások,
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80 mg vas(II)-szulfát
80 mg mukoprotein
30 mg aszkorbinsav

0,35 mg folsav

jellemzői:

nagyobb hatékonyság:
- a folsav azonnal felszabadul, a vasionok felszabadulása elnyújtott
- a felszívódás jelentősen javul

kiváló tolerabilitás, megnövekedett compliance:
- napi 1 tabl. bevétele elegendő enyhe anaemia esetén
- a mukoprotein csökkenti a mellékhatások előfordulásának gyakoriságát

Alkalmazási előírás

Nyújtott hatású vaskészítmény, mely kis mennyiségben folsavat is tartalmaz.
A mucoprotein hozzáadása késlelteti a vas felszabadulását, ily módon megakadályozza túlságosan nagy vaskoncentráció kialakulását, ez csökkenti a mellékhatások gyakoriságát.
Alacsony haemoglobin szint (kb. 100 g/l) normalizálásához (< 150 g/l) napi két drazsé adásával 2 hónapos kezelésre van szükség, de a vasraktárak feltöltődése legalább 3 hónapos kezelés után várható.

Hatóanyagok: 80 mg ferrum (256,3 mg ferrosum sulfuricum sesquihydricum alakjában), 0,35 mg acidum folicum (0,39 mg natrium folicum alakjában) retard drazsénként. Segédanyagként: 80 mg mukoproteint és 30 mg ascorbinsavat tartalmaz.
Színezőanyag: Erythrosin.
Javallatok: Latens vashiány, ill. vashiányos anaemia folsavhiánnyal (pl. terhességben).
Ellenjavallatok: Fokozott vastárolással járó kórfolyamatok: haemochromatosis, haemosiderosis, vasfelhasználási zavarok, sideroblastos anaemiák, thalassaemia, nem vashiányos anaemia; B12 hiányos megaloblastos anaemia. Gyermekkor.
Adagolás: Felnőtteknek:
Enyhe vashiányos anaemiák és latens vashiány: napi 1 retard drazsé szétrágás nélkül, reggeli előtt. Súlyos vashiányos anaemiák: naponta 2-szer 1 retard drazsé szétrágás nélkül, reggel és este 1/2-1 órával étkezés előtt.
3 hét múlva az adag napi 1 drazséra csökkenthető.
A vasraktárak feltöltéséhez a vasterápiát a haemoglobin értékek normalizálódása után még 1-3 hónapon át folytatni kell (napi 1 drazsé reggeli előtt), egészen addig, amíg a serum ferritin tartalma el nem éri a megfelelő szintet.
Mellékhatások: Ritkán enyhe gastrointestinalis panaszok (gyomorfájdalom, hányinger, hányás, meteorismus, székrekedés, vagy hasmenés). Egyes esetekben allergiás reakciók.
Gyógyszerkölcsönhatások: Együttadása tilos:
- dimerkaptollal (toxikus komplexet képez).

Együttadása kerülendő:
- tetraciklinekkel, penicillaminnal, ciprofloxacinnal, acetohidroxamsavval (kelát képződés miatt a vasfelszívódás csökken),

- cholestyraminnal (csökken a vasfelszívódás),
- alumínium-, magnezium-, kalcium só tartalmú antacidumokkal, foszfátokkal és karbonátokkal (vasfelszívódás csökken),
- cimetidinnel (csökken a vasfelszívódás).

Ezek a gyógyszerek és a vas bevétele között legalább 3-4 óra teljen el.
Figyelmeztetés: Mint más vaskészítmény, a Tardyferon Fol a székletet sötétre festi, és így melaenát utánozhat.
Diagnosztikus vizsgálatokat befolyásolja. A benzidin teszt, vagy más occult bélvérzés kimutatására szolgáló vizsgálatok álpozitív eredményt adhatnak. A Tardyferon Fol adását legalább 3 nappal ezen vizsgálatok végzése előtt fel kell függeszteni.
Túladagolás: (mérgezés)
Az előírás szerinti adagolású Tardyferon Fol kezelés nem okozhat túlzott vasfelvételt.
Véletlen túladagolás, főleg téves lenyelés gyermekekben mérgezést okozhat.
A vas toxicitás küszöbértéke gyermekeken sokkal alacsonyabb, már 2 g per os adása súlyos, néha halálos mérgezést okozhat.
A vasmérgezés tünetei:
Első tünetek: kávéaljszerű hányással kísért haemorrhagiás gastritis, erős gyomorfájdalom, esetleg hasmenés, később székrekedés.
Későbbi tünetek: collapsus, acidosissal kísért convulsiók és néha toxicus hepatitis.
Kezelése: a túladagolt vas lenyelése után röviddel meg kell hánytatni a beteget.
Ezentúl nyers tojás és tej adásával - amely vas complexeket képez -, csökkenthető a vas felszívódása. A túladagolt vas lenyelése után egy órán belül kell gyomormosást végezni 1 %-os bicarbonát oldattal. Deferoxamin (Desferal inj. Ciba) /kelátképző szer/ használható antidotumként súlyos mérgezésben.
Folsav túladagolása nem fordulhat elő, mivel a Tardyferon Fol csak igen kis mennyiséget tartalmaz.
Eltartása: 25 °C alatt fénytől védve.
Megjegyzés + Orvosi rendelvényre.
Csomagolás: 30 db kerek élénk rózsaszínű retard drazsé, törési felülete szürkésfekete. (Robapharm)
Alk. ei. OGYI eng. száma:6145/40/94.

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Endometrium carcinoma: general indications of low dose-rate brachytherapy, Institut Gustave-Roussy experience

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INTRODUCTION The main treatment of endometrial carcinoma is surgery, but the peculiar medical status of patients and/or the extent of the disease do not always allow a radical surgery. Even when this surgery can be performed, the local recurrence risk remains between 10 and 15%. This recurrence rate can be notably decreased with complementary radiotherapy. So many authors think that the best treatment for endometrial cancer is a combination of radiotherapy and surgery. The limits of both treatment must be clearly defined in order to avoid a possible added toxicity leading to an increased morbidity.

In practice, three therapeutic groups can be defined according to stage of the disease and medical status of the patient:
– *group A:* surgery is the main treatment, the aim of radiation is only to increase the local control: local recurrences are decreased from 10-15% to less than 3%.
– *group B:* patients are not operable, treatment consists in combination of external radiotherapy and brachytherapy.
– *group C:* medical status of the patients does not allow a carcinologically satisfactory radical surgery, radiotherapy will have to compensate for this lesser surgery to obtain an equivalent result.

GENERAL INDICATIONS OF BRACHYTHERAPY According to the three predifined groups, brachytherapy can be included in different protocols: combined with surgery and/or radiotherapy, brachytherapy alone and salvage brachytherapy.

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COMBINATION OF EXTERNAL RADIOTHERAPY AND BRACHYTHERAPY, OR BRACHYTHERAPY ALONE Indications of the Institut Gustave-Roussy (IGR) for *external beam and brachytherapy* are the following:
– patients with stage I (high grade), stage II or early stage III, with poor medical status are treated with a combination of external radiotherapy and brachytherapy if surgery is contraindicated.
– patients with advanced stage III or stage IV are treated with a combination of radiotherapy and brachytherapy whatever the medical status.
Brachytherapy alone is performed when patients have stage I low-grade endometrial tumors with poor medical status.

SALVAGE BRACHYTHERAPY Salvage brachytherapy can be realized either after surgery alone or after radiosurgical treatment.
After surgery alone: in case of a pelvic recurrence, brachytherapy can be combined with surgery and external irradiation. In case of a vaginal recurrence, brachytherapy can be associated with external irradiation or can be performed alone. Interstitial techniques like guide gutter or plastic tube techniques are especially useful.
After radiosurgical treatment: in case of a pelvic recurrence, the main treatment is surgery which can be combined with preoperative brachytherapy. In case of vaginal recurrence, brachytherapy must be discussed: its modality depends on the previously delivered doses and location of this vaginal recurrence. Lateral and anterior walls of the vaginal cavity are the best indication for interstitial techniques.

RADIO-SURGICAL TREATMENT The actual IGR treatment protocol is based on two retrospective studies about endometrium carcinoma stages I and II. The first one compared one group of patients (59 cases) treated by radiation alone (medical contraindications to surgery) to another group (68 cases) treated by combination of radical extended surgery and irradiation („full" dose of preoperative utero-vaginal brachytherapy with the aim of complete tumor sterilisation). The 5-year survival rate

was 84% for patients treated by radio-surgical combination and 42% for patients treated by radiotherapy alone. For patients treated by radio-surgical combination causes of death were: cancer 3%, severe therapeutic complications 7%, intercurrent diseases 6%. For patients treated by radiotherapy alone, causes of death were: cancer 12%, severe therapeutic complications 2%, intercurrent diseases 27%. The low-grade complication rate was 19% in the first group and 15% in the second group. In total, for patients treated with a radio-surgical combination, the cancer control rate was better but the incidence of complication was too high. Consequently, it was decided to increase the indications of radio-surgical combined treatments, while respectively decreasing the importance of each specific therapeutic method.

After this first retrospective study, our protocol was modified taking into account its findings. To illustrate this therapeutic evolution, a second retrospective study was done. Between 1971 and 1979, 151 patients with stage I (90%) and II (10%) endometrial cancer were treated with a radio-surgical combination. The aim of this study was to assess the value of brachytherapy. The judgement criteria were the complication and local control rates. The treatment consisted in pre-operative brachytherapy: vaginal alone (upper-third) in 55% cases and vaginal + uterine in 45% cases followed by bilateral salpingo-oophorectomy and hysterectomy (BSOH) + obturator node picking for stage I and by BSOH + partial colpectomy + external iliac lymphadenectomy. The results obtained in terms of local control were identical, whatever the type of brachytherapy: 1,4% vaginal recurrences, 3.5% pelvic recurrences. Operative difficulties were linked to brachytherapy are the following: the delivered dose was too high in 3 cases, and in 1 case the time delay between brachytherapy and surgery was not respected: surgery was performed 3 weeks after the end of brachytherapy, when the inflammatory reactions are at their most. Postoperative complications occured in 10 cases (7%). They were: 4 uretero-vaginal fistulae, 1 peritonitis and 5 lymphocysts.

Actual IGR protocol This second study lead us to our present treatment protocol which consists of the following:

Stage I disease

1. vaginal brachytherapy immediately followed by surgery, 2. BSOH + obturator node picking, 3. complementary external radiotherapy in case of poor prognostic factors: myometrial infiltration, nodal involvement, ovarian metastasis, grade 3 tumours.

Stage II disease

1. vaginal or utero-vaginal brachytherapy (if endocervical involvement is important) immediately followed by surgery 2. BSOH + external iliac lymphedenectomy and 3. complementary external radiotherapy as for stage I.

In this combined radio-surgical treatment, several questions, however, remain to be answered.

- When should the brachytherapy be done, pre or postoperatively?
- What should the target volume be?
- Which of many techniques to use?
- What dose to give?
- Where to prescribe it?
- What time interval between brachytherapy and the surgery?

PRE- OR POSTOPERATIVE BRACHYTHERAPY? It is possible to answer the first of these questions by looking at the results of the retrospective studies (briefly mentioned before).

When brachytherapy is performed before surgery, the delivered dose to the critical organs are very low *(Table 1);* the surgical difficulties rate, linked to preoperative brachytherapy, is less than 3%; the postoperative complication rate is low *(Table 2).* There is a risk of a partial change in the pathological information brought by the surgical specimen, especially if an utero-vaginal brachytherapy is performed 6 weeks before surgery. This risk of loss of prognosis factors does not exist if brachytherapy is performed immediately before surgery and furthermore if only vaginal brachytherapy is performed.

When brachytherapy is applied after surgery, a 6-week delay must be allowed for scar healing. During this time, the prognostic factors can be brought together: myometrial infiltration, endocervical invasion, nodal involvement and ovarian metastasis. The dose delivered postoperatively to small bowel, which has come down in the pelvis in the absence of the uterus, cannot be systematically calculated because of the difficulty in evaluating the exact position of small bowel. This can increase the risk of digestive complications and to try to prevent these complications can lead to deliver an insufficient vaginal

Table 1. Brachytherapy combined with surgery for stages I and II (mean doses to critical organs of 166 patients)

	Brachytherapy dose in Gy	
	Rectum	Bladder
Preoperative		
vaginal	24	25
uterovaginal	29	33
Postoperative	37	46

Table 2. Brachytherapy combined with surgery for stages I and II pre- and postoperative problems)

Surgical difficulties	
Cancer invasion	1%
Brachytherapy	2.5%
Miscellaneous reasons	10%
Postoperative complications	
Peritonitis	1%
Ureterovaginal fistulae	2%
Lymphocysts	4%

brachytherapy dose. Post-operative brachytherapy can be optimized in selected cases of high risk vaginal recurrences, which are correlated to the known prognostic factors.

VAGINAL OR UTERO-VAGINAL BRACHYTHERAPY? In 80 to 90% of cases, vaginal recurrences of endometrial carcinoma occur at the vaginal vault. The target volume for a prophylactic brachytherapy should therefore be the superior third of the vagina in stage I and the cervix and uterine isthmus have to be added in stage II.

As mentioned above, the second retrospective study showed identical local control rates for vaginal or utero-vaginal brachytherapy. The irradiated volume was larger for utero-vaginal brachytherapy with an increase in the dose to critical organs: 5 Gy more to the rectum, 8 Gy more to the bladder and 3 Gy more to external iliac nodes. Preoperative utero-vaginal brachytherapy can also lead to a modification of important histologic prognostic parameters (tumour differentiation, degree of myometrial infiltration and cervical extension). Also, when brachytherapy is only vaginal, the protection of the zone irradiated by brachytherapy is particularly easy when postoperative external beam radiotherapy is indicated.

TECHNIQUES? Several brachytherapy techniques for endometrial cancer have been developed and are used today around the world. The IGR brachytherapy technique is based on a case by case adaptation permitting personalization of each brachytherapy application at the level of the application itself as well as a perfect knowledge of the dose distribution to the target volume and the adjacent normal structures which have to be spared. The second important aspect of the IGR technique is the necessity of total radioprotection of the staff.

For vaginal brachytherapy

- a vaginal mould applicator is made individually for each patient. This applicator therefore follows exactly the contours of the vagina and of the cervix for each patient.
- the use of miniaturized low-dose rate 137 Cs sources of which the length and position are chosen for each case allows an adapted irradiated volume.
- a remote afterloader, Curietron type, permitting complete radioprotection but also an adaptation case by case because of the programming and mobility of the sources,
- and finally, a computer calculates the dose distribution to any anatomical point, plane or volume.

For utero-vaginal or cervico-vaginal brachytherapy

- the individually prepared vaginal mould is also used, as well as the other equipment mentioned above.
- and a single uterine source is added.

Other techniques are:

- vaginal mould applicator: Iridium, manual afterloading (Pierquin),
- Bloedorn-Delclos applicator,
- disposable Delouche applicator,
- Fletcher, Raynal, Baillet...

WHAT DOSE TO GIVE? The ICRU recommendations for specification of absorbed dose and irradiated volume in intra-cavitary brachytherapy are for cervix carcinoma brachytherapy. These recommendations can be applied to endometrial carcinoma brachytherapy. The role of brachytherapy is prophylactic and it is therefore logical to deliver a dose of 50 Gy. The volume irradiated to a minimum dose of 50 Gy will constitute the reference volume like the one irradiated to 60 Gy in brachytherapy for cervix carcinoma as recommended by the ICRU. For stage I, a minimum dose of 50 Gy is delivered at 0,5 cm of the mucosal surface of the superior 1/3 of the vagina. The same dose to 0,5 cm around the cervico-isthemic region is added for stage II.

WHAT INTERVAL BETWEEN BRACHYTHERAPY AND SURGERY? When the brachytherapy is preoperative, it should be done immediately before the surgery because it will then induce little modification of important histopathological parameters and the whole treatment can be administered in the same hospitalization (if external radiotherapy is not needed afterwards). Immediate surgery does not lead to higher operative or postoperative complications. In case of postoperative brachytherapy, it will be performed approximately 6 weeks after the surgical intervention to permit sufficient vaginal vault scar healing.

INSTITUT GUSTAVE-ROUSSY RESULTS The last study realized at Gustave-Roussy was done on 325 patients with adenocarcinoma of the endometrium, stages I and II, treated between 1976 and 1986. All these patients were operated but 4% were treated by surgery alone without brachytherapy. For the great majority of this population treated by combined radio-surgical approach, brachytherapy was performed before surgery in 73% of patients. After the surgery 30% of patients received a complementary external beam irradiation (with an adapted protection according to the volume previously irradiated by brachytherapy) in case of bad prognostic factors. *The overall 5-year survival* rate was 83.3% for stage I and 58.2% for stage II. In function of the other prognostic factors, the 5-year survival rate was different: 92.4% when the myometrial infiltration was less than half and 61.4% in other cases. For nodal histological involvement, the survival rate decreased from 90.5% for N- to 55% for N+.

Amongst the 325 patients of this series, there were 21 *recurrences*: 11 peritoneal, of which 3 were associated with pelvic disease, 2 paraaortic, 2 pelvic alone and only 6 vaginal. Out of these, 6 patients received vaginal brachytherapy. So in the combined radio-surgical treatment, the vaginal recurrence rate was 0.6% (2/312).

Because of the adapted therapeutic approach case by case for brachytherapy as surgery, and because of the adaptation of each treatment to the other one, the complication rate is considerably low. In addition to the adaptation of each treatment to the other, the magnitude of each modality was decreased over the years, going from a „full" dose utero-vaginal brachytherapy with Wertheim type hysterectomy to the actual individualized

protocol leading to a low complication rate. In the IGR series described above, the *postoperative complication rate* was 15% (50/325). The risk was related to the type of surgery, being rarely found when a simple total hysterectomy + obturator node picking was done. For the patients who had a pelvic lymphadenectomy, the major complication was hemato or lymphocele which necessitated surgical drainage in 38 patients (11%).

Another group of 206 patients in Tours treated with a comparable protocol has been examined to also determine the complication rate of combined radio-surgical treatment in endometrial carcinoma. The brachytherapy technique employed was similar to the one at IGR except that the preoperative brachytherapy was more often utero-vaginal. The surgical procedure was also more radical, being a CHL in 66% (136/206). The complications were described in 2 groups: immediate i.e. during the brachytherapy application and late. During the brachytherapy application, 6 patients presented the following problems: 1 deep venous thrombosis, 2 infectious, 1 other and 2 unknown. Twenty-one patient (10.2%) presented „late" complications. Seventeen in the utero-vaginal brachytherapy group and 5 in the vaginal brachytherapy group. The majority of these complications were urinary or vascular. Eight of the 10 urinary complications were of urinary incontinence which can probably be related to the surgery. There were 2 cases of cystitis. The vascular complications were: 5 cases of lower limb edema (uni or bilateral), 2 phlebitis and 1 case of „heavy legs" sensation. The other complications were: 4 digestive, 3 gynecologic or pelvic and 1 neurological. All these complications were graded according to Chassagne's glossary of complications: 3 grade 1 (11.6%), 22 grade 2 (8.6%), 1 grade 3 (3.8%), 0 grade 4 (0%). It is to be noted that in 11 of these complications, an important contribution to the morbidity could be found in the patient's past medical history and/or because of a more aggressive treatment (surgery and/or radiotherapy) than the majority of the patients in the series. This very detailed study on complications shows the necessity of decreasing brachytherapy and surgery when possible to obtain the same local control but with a lower complication rate.

CONCLUSION

– surgery remains the main treatment of endometrium carcinoma,
– a combined radio-surgical treatment allows a very high local control rate,
– brachytherapy and surgery must be adapted to each other and case by case to decrease the morbidity.

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Endometrial carcinoma – adjuvant locoregional radiotherapy

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INTRODUCTION Carcinoma of the endometrium is increasing in incidence in developed countries and now exceeds the incidence of carcinoma of the cervix in several. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) is recognised as the single most important element of therapy in stage I and II disease. However, the role of adjuvant post-operative radiotherapy either as external beam or as intracavitary therapy to the vaginal vault has not yet been clearly proven.

THE ROLE OF POST OPERATIVE RADIOTHERAPY Improved survival following adjuvant radiotherapy has not yet been established. Only two early studies have reported a survival advantage. *Nolan et al.* (1) in 1967 retrospectively demonstrated improved survival and local control with radiotherapy and surgery versus surgery alone in patients with larger and less differentiated tumours. *Graham et al.* (2) in 1971 in a prospective study reported a 5-year survival rate of 64% (21/33 patients) in stage I patients receiving hysterectomy alone. This was significantly worse than patients receiving additional pelvic irradiation – 88% (80/90 patients). Radiotherapy also reduced the pelvic recurrence rate from 12% (4/33) to 1.1% (1/90). In the GOG study of 766 patients (3) the pelvic recurrence rate in the surgery only patients was 31.8% (101/320) and radiotherapy group 16.8% (62/368), despite the latter group having significantly higher histological grade of tumour and deeper invasion of the myometrium. In a retrospective study of 384 patients with stage I disease, high risk patients were offered radiotherapy (4). Twenty-eight of these, however, violated protocol and did not receive radiotherapy. There was a significant increase in pelvic recurrence rate in these patients (14.3% versus 3.9%). Although there are no recent trials randomising patients into a no radiotherapy arm, further inference on the benefit of external beam radiotherapy can be made from trials which have compared intracavitary therapy alone versus combined intracavitary and external beam treatment. A summary of these trials is presented below but the most significant of these was reported by *Aalders et al.* (5) in 1980 who reported a significantly lower pelvic recurrence rate (1.9% versus 6.9%) with the combined approach.

Table 1. Incidence of positive pelvic lymph nodes in patients with stage I and II endometrial carcinoma. Summary of three lymphadenectomy series (18, 19, 20).

	Incidence of positive pelvic nodes (%)			
Grade	Creasman et al (1987)	Quinn et al (1995)	Calais et al (1994)	Summary
1	5/180 (3%)	7/43 (16%)	5/74 (6.8%)	17/297 (5.7%)
2	25/288 (9%)	11/92 (12%)	5/59 (8.5%)	41/439 (9.3%)
3	28/153 (18%)	13/103 (12%)	4/22 (18.2%)	45/276 (16%)
Myometrial invasion				
none	1/87 (1%)	1/18 (5.6%)	0/0 (0%)	2/105 (2%)
<1/3	15/279 (5%)	11/70 (15.7%)	6/97 (6.2%)	32/446 (7%)
mid 1/3	7/116 (6%)	1/70 (1.4%)	4/43 (9.3%)	12/229 (5.2%)
>2/3	35/139 (25%)	18/80 (22.5%)	4/15 (26.6%)	57/254 (24%)
All stage I	58/621 (9.6%)	31/238 (7.0%)	5/107 (4.7%)	94/966 (9.7%)
All stage II	-	10/45 (22%)	9/48 (19%)	19/93 (20%)

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Table 2. Correlation of tumour grade with depth of myometrial invasion (19, 21).

Myometrial invasion	FIGO grade 1	2	3
No invasion	58%	52%	38%
< 1/2 myometrial invasion	30%	28%	16%
> 1/2 myometrial invasion	12%	20%	46%

Table 3. Percentage 5-year disease-free survival for surgical stage I endometrial carcinoma (22).

Myometrial invasion	FIGO grade 1	2	3
No invasion	96%	92%	85%
< 1/2 myometrial invasion	95%	90%	69%
> 1/2 myometrial invasion	81%	70%	42%

EXTERNAL BEAM (EB) ALONE VERSUS INTRACAVITARY (IC) ALONE. *Sala* and *del Regato* (6) in 1969 retrospectively compared 40 Gy EB to the pelvis (70 patients) to 60Gy IC to the vaginal vault (48 patients). There were no vaginal recurrences in either group and the 3-year survival rates were similar (87% versus 77%). *Latini* (7) in 1990 retrospectively compared 131 stage I patients who received 45-50Gy EB, post-operatively to the pelvis with 29 patients who received 50 Gy to the vaginal vault by intracavitary therapy. The 5-year survival rates were similar (88% versus 83%) and there was no significant difference in the pelvic recurrence rates (2% versus 0%).

Weigensberg et al. (8) in 1976, in a small randomised trial, compared 40Gy EB to the pelvis (38 patients) to 54Gy IC to the vaginal vault (53 patients). Survival rates were similar but the pelvic recurrence rate was significantly higher in the EB alone group (9% versus 2%, p=0.01).

Morrow et al. (3) further analysed the GOG study in 1991 and demonstrated that a higher proportion of recurrences were vaginal following EB alone rather than IC alone. None of the 3 pelvic recurrences in 78 patients who had IC treatment were vaginal, whereas 7 of 95 recurrences (7.4%) out of 368 patient treated with EB were vaginal.

EXTERNAL BEAM ALONE VERSUS COMBINED EXTERNAL BEAM AND INTRACAVITARY *Torrisi et al.* (9) in 1989 reported a series of 73 patients who received post-operative EB only at doses of between 45Gy to 50Gy. They had either grade 2 or worse histology or deep myometrial invasion. The 5-year actuarial survival was 90%, disease-free survival was 82% and the local relapse rate was 6.5%. These figures are similar to series which have used combined IC and EB in comparable cases (4,10,11, 12,13). *Bliss et al.* (14) in 1992 retrospectively compared 40 patients who received 40-45Gy EB to the pelvis with 51 patients who, in addition, received 50Gy to the vaginal vault mucosa by IC therapy. The vaginal vault recurrence-rate was significantly higher in the patients who received EB alone (4 versus 0), despite these patients having significantly lower stage disease. However, bowel toxicity and vaginal stenosis was higher in the combined treatment group.
There have been no randomised trials in this category of patients.

INTRACAVITARY ALONE VERSUS COMBINED INTRACAVITARY AND EXTERNAL BEAM *Bedwinek et al.* (15) in 1984 in a small retrospective review evaluated patients with stage I, grade 3 disease. There was no significant difference in the pelvic recurrence rate between 33 patients treated with IC alone (20-45Gy) compared to 50 patients who received IC and EB (20-50Gy) (12% versus 8%). The radiotherapy doses and techniques varied widely but on further analysis, there was a correlation between IC dose and pelvic control rate. *Aalders et al.* (5) in a randomised trial compared 227 patients who received IC alone (60Gy to the vaginal wall) with 263 patients who, in addition, received EB (40Gy) to the whole pelvis. The reported survival rates were similar but the combined approach demonstrated significantly lower pelvic recurrence rates (1.9% versus 6.9%).

Table 4. The Royal Marsden protocol for stage I endometrial cacinoma post TAH and BSO.

Myometrial invasion	FIGO grade 1	2	3
No invasion	0	0	EB&ICa
< 1/2 myometrial invasion	ICb	ICb	EB&ICa
> 1/2 myometrial invasion	EB&ICa	EB&ICa	EB&ICa

EB = External beam (45Gy in 25f, daily), ICa = 2 x 4 GY @ 0.5cm, ICb = 4 x 5.5 Gy @ 0.5cm.

CONCLUSION Post-operative adjuvant radiotherapy is now commonplace in the management of patients with endometrial carcinoma. Standard treatment protocols, developed empirically, have generally placed patients into high, intermediate and low risk categories, based on histological prognostic factors (Tables 1, 2, 3). The high risk group receiving EB and IC, intermediate IC alone and the low risk group surgery alone (Table 4.). With such a scarcity of randomised trials it is no surprise that there are appreciable differences between medical centres with respect to patient selection, treatment methods and timing of adjuvant radiation therapy. For example, there are reports favoring the routine use of adjuvant radiotherapy for all grades of endometrial carcinoma even with minimal myometrial invasion (16, 17). A recent informal questionnaire of radiotherapy centres in the UK, conducted by the British Institute of Radiology, showed no consensus in the criteria for designating a patient with stage I endometrial cancer into a no risk, low risk or high risk group. In addition, there was no agreement on which patients should receive intracavitary therapy, external beam

treatment or a combination of the two. The commonest policy was that adjuvant radiotherapy is offered to all patients with poorly differentiated tumours and to those with well to moderately differentiated tumours invading more than halfway through the myometrium.

In conclusion, the impact of adjuvant radiotherapy on survival requires further evaluation with randomised trials. There is good evidence, however, that local failure is reduced by intracavitary and external beam radiotherapy. Combined radiotherapy appears to be more effective than either external beam or intracavitary radiotherapy alone, albeit at the expense of higher toxicity. Further substantiation is required especially addressing the question of EB alone against combined EB and IC where no randomised trial exits. To achieve this common criteria for defining no risk, low-risk and high-risk tumours are needed.

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Current status of preoperative and adjuvant irradiation in endometrial cancer

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INTRODUCTION Cancer of the endometrium is the most common genital malignancy in Slovenia with the incidence of 24/100,000 women (1). Endometrial cancer has been considered a lesion which can be successfully treated especially because about 80% of these tumors are diagnosed at stage I confined to the uterine corpus. The Annual Report on the results of treatment in gynecological cancer indicates the absolute 5-year survival rate to be 72.7% (2). Surgery with adjuvant radiation therapy has been the traditional management of endometrial cancer and has generally provided high cure rates, especially in stage I (about 90%). Nevertheless, for adjuvant radiation therapy a considerable controversy exists regarding the mode (internal and/or external), the timing (preoperative and/or postoperative), and the real effect of this therapy. Except for surgery, it has not yet been found that one treatment policy improves survival to a higher extent than the other. Further, the risk for complications caused by the adjuvant radiation has to be considered. The frequency of preoperative radiotherapy, either the classical Heyman packing method with radium or the afterloading technique with cesium, has diminished since the adoption of surgical staging that also requires surgical evaluation of the intraabdominal status and lymph nodes.

The knowledge of prognostic factors permits a rational therapeutic approach in various stages. The most important prognostic factors in endometrial cancer are:

- cancer spread (clinical stage)
- histologic type
- histologic grade
- depth of myometrial invasion
- lymph node metastasis
- age.

Some data demonstrate that the ploidy of the tumor is also an important independent prognostic factor (3). The most important adverse variable is lymph node metastasis which correlates with grade of the tumor, depth of myometrial invasion and cervical involvement. The classification of endometrial cancer into low risk and high risk groups is made according to the prognostic factors. Low risk group involves the cases limited to the uterine corpus (stage I), and those in whom cancer infiltrates only the inner half of the uterine wall (stages Ia and Ib according to the FIGO surgical classification), and the cancers are highly or moderately differentiated adenocarcinomas, with or without metaplasia. The high risk group involves women with histologic grade 3 cancers with or without any myometrial invasion or any histologic grade with invasion greater than half of the myometrium and/or positive nodes. The histologic types adenosquamous, clear-cell and papillary type belong to the high risk group.

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LITERATURE REVIEW To date, there has been no prospective randomized trial demonstrating that preoperative and/or postoperative pelvic radiation offers a survival advantage comparing to surgery done. In his review *Jones* (4) found no difference between the 5-year survival rates for patients with stage I disease treated by surgery alone (75%) or by combined therapy (78%), but from his analysis it is not clear whether high risk cases comprise a greater percentage of the combined treatment group. The study of *Aalders et al.* (5) demonstrated that patients who received only vault irradiation had a 6.9% vaginal recurrence rate, whereas the patients who received vault irradiation in combination with additional whole pelvis external irradiation had only 1.9% of vault recurrences. His observation was that postoperative vaginal brachyradiotherapy alone was ineffective in eliminating local recurrence, and besides this, that there was no improvement in overall survival and recurrence rates with the use of external pelvic radiation. The only group (constituted of only 17% of all patients), which seemed to have a survival benefit of postoperative external irradiation in about 10%, was the group with grade 3 disease and deep myometrial invasion. The conclusion of *Aalders* (5) *and other investigators* (6-8) was that with radiation therapy there was a reduction of pelvic recurrence rate, but the distant metastasis rate was higher, so pelvic radiation therapy contributes merely to the changed pattern of recurrences. The overall 5-year survival for recurrent endometrial cancer ranges from 10% to approximately 30% (6, 8). The extent of pelvic recurrence

(vaginal vs. extravaginal disease) was the most important predictor of survival. Patients with the recurrence confined to the vagina have a relatively good possibility of salvage with agressive local therapy (9, 10). In the study of *Poulsen et al.* (10) no postoperative radiation was given in stage I low risk cases and the incidence of recurrence was 7%; with postoperative external radiation the incidence of recurrence was 15% in high risk stage I cases, and 29% in stage II cases. The vaginal recurrence in low risk cases were subsequently successfully treated with radiation, and only 4.4% of patients died of the diseases during the following 5-year period. Thus, the conclusion of *Poulsen* (10) *and other authors* (8, 11) is that surgery alone is the adequate treatment for low risk cases and that primary adjuvant radiation should be reserved for high risk group of endometrial cancer.

The extension of endometrial cancer into the cervix (stage II) implies a lower survival rate because of increased lymph node involvement (20-25%). These patients should first undergo surgery, and after that the postoperative radiation treatment can be tailored to the other risk factors.

In combined treatment the risk of complications caused by the radiotherapy should be considered. *Elliott et al.* (12) reported 14.4% of some kind of local radiation complications, and 3% of patients had severe complications such as rectovaginal fistula. *Corn et al.* (13) referred a significant increase in severe complication rate (5.5%), especially bowel obstruction, in irradiated patients who had prior lymph node dissection. On the contrary, in an analysis by *Homesley et al.* (14) there was no increase in radiation complications after hysterectomy with pelvic and periaortic node dissection, compared to patients treated with hysterectomy without node dissection.

OUR EXPERIENCE The most common surgical approach in endometrial cancer is total abdominal hysterectomy with bilateral salpingo-oophorectomy (THBSO). Ever since *Novak* (15) in 1953 described pelvic node metastasis in cases of endometrial cancer, the most common operation in endometrial cancer at our Department had been classical Wertheim (Piver II). Only in the last decade the surgical radicality has diminished according to surgery recommended by many oncological centers.

We have combined the surgery with irradiation in almost all cases. Over the last two decades preoperative radiotherapy has practically not been applied anymore, because of the necessity to adopt surgical staging to determine prognostic factors for postoperative irradiation. In low risk cases the postoperative radiation consists of vaginal vault irradiation to the dose of 4000 cGy along a reference isodose line 1 cm beyond the vaginal mucosa. In high risk group and in lymph node metastasis cases a dose of 5000-5400 cGy is delivered in 4 weeks to the whole pelvis. The results of peritoneal cytology have not modified our treatment policy, because we think that peritoneal cytology is not an independent prognostic indicator.

The surgical procedures for 492 patients treated in the period 1983-90 at our Department are presented in *Table 1.*

Table 1. Endometrial cancer: Surgical treatment (1983-90)

	N	%
Wertheim classical (Piver II)	201	41
Hysterectomy abdominal	243	49
- with lymphadenectomy	135	
- without lymphadenectomy	108	
Hysterectomy vaginal	48	10
Total	492	100

Surgery consisted of classical Wertheim operations in 201 cases (41%) and simple THBSO in 291 cases (59%). Pelvic lymphadenectomy was performed in all cases of Wertheim procedure and in 135 cases (55%) of abdominal THBSO. Vaginal THBSO was done in 48 patients (10%), usually in very fat patients and in those at surgical risk.

Table 2. Endometrial cancer: 5-year survival (1983-90) according to stage

Stage	N		Survival N	Survival %
I	433	(88%)	366	84.5
II	35	(7.1%)	23	65.7
III	21	(4.3%)	9	43
IV	3	(0.6%)	1	33
Total	492		399	81

Table 2. shows the 5-year survival according to the stages and the total survival rate of 81%.

Table 3. Endometrial cancer: 5-year survival according to adjuvant radiotherapy

Radiotherapy	N		Survival N	Survival %
Preoperative	3	(0.6%)	1	33.3
Vaginal	279	(56.7%)	243	87.1
External	185	(37.6%)	135	73.0
None	25	(5.1%)	20	80.0

Table 3. shows the type and percentage of adjuvant radiotherapy with the respective 5-year survival. Low risk cases with vaginal irradiation had the survival rate of 87.1%, high risk cases with external irradiation 73%, that is, of course, significantly worse. 5% of patients did not receive any radiotherapy, because either no more cancer tissue was detected in the surgical specimen, or because they refused irradiation.

Vaginal recurrences were observed in 3.9%, only in cases in whom the invasion was more than half of the myometrium. All these patients received external radiation, but all died.

In stage I cases there were 3%, and in stage II 20% of positive pelvic lymph nodes. The 5-year survival in cases of negative nodes was 88%, in cases of positive nodes 56%.
Only 15% of cases belonged to grade 3 group where the 5-year survival was 65.8% in contrast with the survival rate of 84.2% in grade 1 and 82.7% in grade 2 cases. The impact on the survival rate of myometrial invasion was high: 69.7% in cases of myoinfiltration more than half, and 88.5% if myoinfiltration was less than half (62% of all patients). These two factors (grade and myoinvasion) are also predictive of lymph node metastases.

Table 4. Endometrial carcinoma stage I: 5-year survival according to surgery

	N	Survival N	%
Wertheim classical	175	163	93.1
THBSO	213	173	81.2
Total	388	336	86.6

P<0.005

Considering only stage I endometrial cancer the 5-year survival was significantly higher in cases of classical Wertheim (93.1%) than in THBSO operations (81.2%) *(Table 4.)*. The difference of survival remained significant also after the correction of age (mean age of patients submitted to Wertheim was 57 years, and of those to THBSO 62 years).

The difference in survival was particularly evident between classical Wertheim and THBSO considering the risk prognostic factors (grade and myometrial invasion).

From our data we may presume that removing more tissue from around the uterus, as is the case of classical Wertheim, one could prevent pelvic recurrences and improve the survival rate, irrespective of routine pelvic adjuvant therapy.

CONCLUSION Because of the overall good survival rate and low incidence of complications most oncological centers continue to use the combined surgical-radiotherapeutical approach in the treatment of early endometrial cancer. But according to some known data regarding the low risk group of patients, where the proportion of relapse is small, and vaginal recurrences can be cured, perhaps routine adjuvant irradiation is not justifiable Unanswered remains especially the question concerning optimal treatment in high risk patients, because prospective randomized studies have been found to be difficult to perform.

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Current status of preoperative and adjuvant irradiation in endometrial cancer: a CTF analysis in Western Europe

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ABSTRACT The aim of this study is to define the clinical-therapeutic approach to endometrial cancer currently being followed in some of the most important centres of reference for gynecological cancer in Western Europe, focusing the role of preoperative and adjuvant irradiation in pathologic T1 (pT1) cases. The analysis of the management of this neoplasia in Western Europe countries shows significant differences regarding some particular clinical conditions. The presence of lymph node spread is generally considered to be the most important prognostic factor, and currently, radiotherapy of the pelvis appears to be the treatment of choice either as the sole postsurgical therapy (57%) or in combination with systemic treatment. An adjuvant treatment in stage I lymph node-negative patients is adopted in the large majority of the centres (70.5%) when poorly differentiated cancer and/or deep myometrial invasion are present. In this condition, radiotherapy appears to be the therapy of choice. The conflicting data which emerge from our research, induce the need of defining common guidelines for standard treatment and large scale multicentric clinical trial concerning the therapeutical choice in particular subgroups of patients with endometrial cancer.

Key words Endometrial carcinoma, diagnosis, treatment.

INTRODUCTION Endometrial carcinoma was once considered a neoplasm with a relatively favourable prognosis because a large number of cases are clinically diagnosed at an early stage, and are therefore limited to the corpus uteri (1-2). In addition, the tumor has a more favourable prognosis than carcinoma of the uterine cervix (1, 3-6) and a lower incidence of lymph nodes metastases in the early stage compared to cervical carcinoma (2, 4). The survival rate for some subgroups of patients (neoplasia of corpus uteri with infiltration only initially involving the myometrium, in the absence of pathological risk factors and if created by adequate surgical therapy), is very high (2, 7). However advanced knowledge of the natural history of endometrial carcinoma, its real potential for lymph node spread and the high level of correction of clinical stage after intensive anatomical-surgical evaluation, have produced a substantial revision of such consideration. As a matter of fact many patients with stage I disease are submitted to various types of adjuvant treatment on the basis of different considerations and risk factors. Radiation therapy either on the pelvis or in combination with brachytherapy on the vaginal vault is often used after surgery with various rationale of application.

Beyond the various definitions of stage (8), other prognostically important pathological factors have been indicated in endometrial cancer which are of considerable importance in the planning of treatment. Among these, histotype (9-10), histological grade (11-13), myometrial invasion (14-17), capillary-like space invasion (18-20), peritoneal cytology (21-24), and lymph nodes metastases (7, 11-12, 25) are currently considered to carry different weight in the definition of prognosis and in the planning of postsurgical treatment.

The aim of this study is to define the clinical-therapeutical approach to endometrial cancer now being followed in some of the most important centres of reference for gynecological cancer in Western Europe focusing the role of preoperative and adjuvant irradiation in pT1 cases.

MATERIAL AND METHODS Data were collected by means of a questionnaire on specific diagnostic and therapeutic options, sent to 115 leading centres for gynecological oncology in Western Europe. There were 82 responses by the end of April 1994 from centres which treated at least 25 cases of endometrial carcinoma per year (mean 44,5; median 30,0; range 25-250).

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The questionnaire focused on the following items: 1) Surgical staging and therapy aiming to define the role and effort in lymphadenectomy, the indications for enlarged and vaginal hysterectomy, the role of peritoneal cytology in the prognosis and treatment planning. 2) The choice of adjuvant treatment in stage pT1 in respect of: stage IC; lymph nodes positivity, hystological grade and hystotype. 3) Treatment modification according to age and menopausal status. 4) Management of advanced stages.

Complete report of the study was already published in European Journal of Cancer (26). This report will focuse the aspects particularly related to adjuvant radiotherapy and preoperative irradiation.

RESULTS

Adjuvant treatment in FIGO stage IC The vast majority of western oncological centres (70/79: 88.6%) consider mandatory a postsurgical adjuvant treatment when deep myometrial infiltration is pathologically documented. Concerning the type of treatment, radiation therapy on the pelvis is predominantly use either alone (63.3%) or in association with systemic treatment (20.3%). Seven centres were involved in randomized clinical trials comparing radiotherapy versus observation or radiotherapy versus chemotherapy (Italian Study Group).

Adjuvant treatment in pT1 lymph nodes negative cases No indication for adjuvant treatment in such condition was declared by 29.5% of centres. Particular indications were recognized by 70.5% of centres such as: poorly differentiated toumors (43) and deep myometrial invasion. Radiotherapy in such cases was the treatment of choice either alone (63.3%) or in combination with systemic treatment (20.3%). Hormons and chemotherapy were rarely adopted, respectively 3.8% and 1.3%.

Adjuvant treatment in pT1 lymph node positive cases All European centres declared to performe adjuvant treatment in such condition Radiotherapy is the treatment of choice either alone (57%) or in combination with systemic treatment (38%).

Indication for brachytherapy of the vaginal vault in pathological stage I neoplasia. Brachytherapy is routinely used in 10 (12.8%) centres, while 20 (25.6%) institutions never perform this therapeutic approach. In 48 institutions (61.5%), the predominant indications for brachytherapy were dictated by poorly differentiated tumours (43.3%), deep myometrial invasion (32.8%) and inadequate surgery (5.9%).

Presurgical radiotherapy in early stages This approach is considered in 16.9% of the centres while in 83.1% of centres there is no indication at all.

DISCUSSION Even though there is general agreement on the usefulness of surgical staging and primary surgery in endometrial cancer, analysis of the management of this neoplasia in Western European countries shows significant differences regarding some particular clinical conditions. The presence of lymph node invasion is generally considered the most important prognostic factor which heavily influences postsurgical decision-making. In fact, there is a general agreement in the adoption of an adjuvant treatment in such a condition. At present, radiotherapy on the pelvis appears the treatment of choice, either as the sole postsurgical therapy (57.0%) or in combination with systemic treatment. An adjuvant treatment in pT1 lymph node-negative patients is given in the large majority of the centres (70.5%) when poorly differentiated cancer and/or deep myometrial invasion are present. In this condition, radiotherapy appears to be the therapy of choice either alone (63.3%) or in combination with systemic treatment (20.3%). Particularly for stage IC, systemic treatment is seldom used. Hormone therapy is given in 3.8% of the centres, even though long term analysis of a randomized study failed to detect any benefit from medroxyprogesterone acetate as adjuvant treatment in such a condition (27).

The conflicting data which emerge from our research concerning the therapeutical choice in particular subgroups of patients with endometrial cancer induce the need of defining common guidelines for standard treatment and large scale multicentric clinical trial for the more controversial aspects.

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Radiotherapy alone for carcinoma of the endometrium

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INTRODUCTION The standard therapy for carcinoma of the endometrium is diagnosis at dilatation and curettage of the uterus (D&C) and subsequent total abdominal hysterectomy and bilateral oophorectomy. This surgery is the main therapeutic manoeuvre for endometrial carcinoma but also serves to allow pathological substaging of the tumour by degree of invasion of the uterus and adnexae and by tumour differentiation. In most centres the need for adjuvant post-operative radiotherapy is assessed on the basis of this pathological staging.

Occasionally patients are seen who are unfit for D&C and hysterectomy. If the patient cannot undergo any form of anaesthesia then the diagnosis has to be made clinically and radiologically and an attempt made to distinguish between a carcinoma of the cervix, uterus or ovary. A histological diagnosis can be obtained by a suction pipette.

More commonly seen is the patient who has undergone D&C and who has suffered ill-effects from the anaesthetic or who proved to be unable to cope with prolonged in-patient care, as in the case of some demented patients. These patients are then referred for radiotherapy with a diagnosis but without having undergone a hysterectomy. Therefore, not only have they been unable to undergo the ideal therapy for this tumour but the substaging is not available to assess the risk of pelvic and paraaortic node involvement.

Furthermore, these patients present a problem to the radiotherapist because of their infrequency, which limits practical experience in managment and, increasingly, also serves to make it difficult to justify to hospital managers the purchase and maintainence of specialised equipment for their treatment.

Historically, patients such as this would have been treated by packing the cavity of the uterus with radioactive material, such as radium in Heyman's capsules (1). However, the decreasing frequency of referral of such patients as anaesthetics have improved and the relatively late adaptation of intrauterine micro-sources to afterloading has resulted in most centres abandoning the traditional method and using more readily available, familiar and safer methods of integrated external beam and intracavitary therapy as they would for carcinoma of the cervix.

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TRADITIONAL METHODS Heyman's capsules were small ovoids containing radium and, later, caesium. They were attached to a string to allow their withdrawal from the uterine cavity after the planned treatment time but were otherwise free to take up any stable position within the uterus. Typically ten to twenty capsules would be packed into the uterus with the intention of stretching the wall of the uterus and ensuring proximity of the endometrial lining and of the tumour to the sources. Because the sources could not be stably orientated in a fixed pattern and because it was not possible to locate the capsules on orthogonal films dosage had to be by milligram-hours with a dose of 8000mgh in two insertions being usual. The technique of insertion to uniformly stretch the uterus was difficult but withdrawal could be worse, with tangling of strings and capsules within the uterus. Good results were obtained using these active source methods with *Anderson et al.* (2) reporting a predicted 5 year survival rate of just less than 50% for a group of 117 patients of mixed stage and histology. Those with stage 1 disease and well differentiated tumours fared best. Interestingly Andersen et al. did not find the addition of external radiotherapy to the intracavitary treatment to be helpful in terms of extending survival. Other workers have also shown good results in using the traditional Heyman's packing method using radium capsules in stage I disease (3).

MODERN METHODS Afterloading with caesium and, more recently, with high activity sources, necessitated the attachment of a source-transfer tube to each capsule which, although flexible, did not allow such freedom of movement of the source within the uterus. This was particularly so with low dose-rate systems for which the transfer tubes had to be of a wide diameter. In common with other afterloading systems, 'the anatomy is made to fit the applicator' rather than the other way around. Nevertheless, this technique can produce good results when used with either low dose-rate or high dose-rate sources (4).

The uterus is approximately the shape of an inverted light-bulb and the uterine cavity is an inverted triangle. Endometrial tissue in the cornua is at the greatest distance from the axis of the uterus. Indeed, it was the finding of a preponderance of recurrences at this site that stimulated Heyman to move away from the Stockholm system of a single intrauterine tube and to develop the capsule method. Nevertheless, many radiotherapists are confined to using a single intrauterine tube and not all the results of this method are bad. *Potter et al.* (5) report a 5 year local control rate of over 75% for patients with stage I disease treated in this manner. However, many centres have tried to adapt their rigid afterloading system to the method of Heyman, with its flexibility and adaptation to the shape of the uterus.

One method of conforming the brachytherapy isodose envelope to the shape of the uterus is to use two curved tubes at 180° to each other running up the lateral walls of the uterus. Such a system can be used with both low dose-rate and high dose-rate sources. A variation on this, if high dose-rate sources are used for multiple fractions, is a single curved applicator used with the orientation of the curve into the right or left cornu alternately for each fraction (6). Whilst with careful source positioning the isodose envelope can approximately match the external shape of the healthy uterus there is no guarantee that the diseased uterus has a cavity shape similar to that of the healthy uterus or that the tumour lies in the high dose area adjacent to the applicators.

If multiple applicators are to be placed in the uterus then the diameter of the cervical os dictates that these are of such a small diameter that miniature high dose-rate sources have to be used.

DOSE There is no universally accepted prescription point or dose when treating the body of the uterus by brachytherapy other than Heyman's capsules. Many radiotherapists aim to give a total dose to the serosa of the uterus of 60-65Gy by fractionated brachytherapy or a combination of external irradiation and brachytherapy. Where CT imaging is available the serosa can be delineated in relation to the applicators and the prescription made to that surface, where CT imaging is not available an estimate has to be made of the position of the serosa and 2cm from the intrauterine sources would be a common estimate.

External irradiation is used if there is obvious involvement of the cervix (stage II disease) or if the tumour is bulky (often accepted as being more than 4cm across). A dose of 40-45Gy in 20-25 fractions is usually delivered to the true pelvis.

A review of the use of high dose-rate brachytherapy for the treatment of unoperated carcinoma of the endometrium is currently in press (4). In this the authors have shown that a policy of brachytherapy alone for unoperated stage I patients and external irradiation followed by brachytherapy for stage II patients has resulted in survival figures as good as those obtained with the traditional low dose-rate Heyman's capsules. Moreover by specifying the dose to the serosa of the uterus or to a point 2cm behind the most posterior capsule they have been able to introduce consistency into their dosimetry. They found the serosa to be most distant from the uterine cavity in the lateral plane, intermediate anteriorly and closest posteriorly. They prescribed either two courses of fractionated high dose-rate brachytherapy to give 30Gy in five fractions to the serosa or point S on each occasion 3-4 weeks apart or, for disease of more than stage I, 40Gy in 20 fractions external irradiation to the pelvis followed by one course of HDR brachytherapy.

CONCLUSION In reviewing the literature on this topic it would appear that whilst a Heyman's capsule-like system probably has the most consistently good results other systems including those that try to conform to the shape of the uterus and those that do not can also be effective. Similarly high dose-rate systems can be as effective as low dose-rate.

There needs to be a generally accepted method of dose prescription, which does not currently exist, if treatment regimens are to be compared for effectiveness. Imaging and flexible source positioning are needed if individualised treatment volumes are to be constructed for each patient. Finally, given the rarity with which this technique is now used a case could be made for specialist centres to offer a regional service in order to maintain experience, collect accurate data and justify the purchase of specialised brachytherapy equipment.

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Exclusive radiotherapy in the management of endometrial carcinoma

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INTRODUCTION The generally accepted management for early stages of endometrial carcinoma is surgery (total abdominal hysterectomy and bilateral salpingo-oophorectomy with para-aortic lymph nodes' sampling) and this strategy should be undertaken whenever feasible. In selected cases with poor prognostic features such as moderately or poorly differentiated carcinoma (G2, G3), deep myometrial infiltration, gross cervical invasion, regional lymph nodes involvement and some histological subtypes, like papillary carcinoma, clear cell carcinoma and adenosquamous carcinoma, surgery is combined with pre- or postoperative radiotherapy. For advanced cases (III and IV stage) exclusive radiotherapy is the treatment of choice.

Radiotherapy alone is also undertaken in selected early cases unsuitable for surgical management due to medical contraindications, e.g. advanced age, marked obesity, hypertension, heart disease, diabetes and phlebitis sequelae and in patients refusing surgery (1-4).

The history of the use of irradiation as a sole management in endometrial cancer is quite lengthy since *Heyman* described in 1929 and 1941 his packing method using Radium as a radioactive source. In that technique uterine cavity was packed as full as possible with multiple (8-12) small Radium preloaded capsules. The technique was particularly suitable for large and irregular uterine cavities. The dose specification was defined in terms of milligrams of Radium inserted for specific number of hours (4-6). In the early 1950's *Henschke* (7) introduced the afterloading technique of intracavitary brachytherapy and in the next 20 years this method generally replaced traditional manual Radium applications. At the same time a gradual shift from LDR to HDR has been noted. In 1934 *Coutard* developed a protracted fractionated dose scheme for external radiotherapy and in 1936 *Paterson* published the results of the treatment of cancer with X-rays (6).

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EXCLUSIVE RADIATION TREATMENT Radiotherapy for endometrial carcinoma nowdays consists of both external beam irradiation and intracavitary brachytherapy delivered in several sequences (4, 6, 8).

EXTERNAL IRRADIATION Whenever possible external radiotherapy should be administered before brachytherapy in order to reduce tumour volume and to improve the geometry for intracavitary application. The *tumour volume* encompasses the whole uterus, cervix, the upper part of the vagina, parametria and pelvic lymph nodes up to common iliac lymph nodes' level. Usually high energy photons of linear accelerators or Cobalt-60 units are used. *Treatment techniques* include two parallel opposed antero-posterior portals 15x15 cm to 16x20 cm or four field „box" method. The *dose is* calculated to bring to the lateral pelvis wall the total external dose of 45-50 Gy and boost up to 55-60 Gy in selected cases of stage III with fractionation 1.8-2.0 Gy/day, 5 times weekly. The treatment is usually individualised as the central area should be shielded after the dose of 20, 25 or 30 Gy depending on the dose of brachytherapy (4-6, 9). Due to significant risk of subclinical paraaortic metastasis expressed by failure rates of 15-20%, selected patients should also be considered for treatment with extended fields encompassing this region (3).

INTRACAVITARY BRACHYTHERAPY An adequate intracavitary brachytherapy should provide the therapeutic dose to the whole uterus and adjacent areas i.e. uterine cervix and upper part of the vagina with the reduced dose in the organs at risk. It is important to determine prior to therapy the size and shape of the uterus and the individual location of other organs. According to *Rotte* (10) brachytherapy requirements for endometrial carcinoma are as follows:

- A dose distribution adapted to the individual situation with dose concentration in the target volume and minimising the dose to the organs at risk;
- A practical technique with regards to radiation protection and to reproducibility of source positioning;

- A dose which minimises clinical complications without reducing therapeutic efficiency.

To meet the above mentioned criteria the following aspects should be taken under consideration: 1. applicators, 2. radioactive sources, 3. calculations and dosimetry.

APPLICATORS Since 1940 different forms of applicators have been developed of which those commonly used for treatment of endometrial carcinoma will be presented.

Endouterine applicators

Modified Heyman packing The classical *Heyman* packing technique was modified by *Simon and Silverstone* in 1976 for Caesium-137 and introduced later into HDR brachytherapy with Iridium-192 as *Heyman-Simon* applicators allowing for individual packing and an individualised dose distribution corresponding to the pathological anatomy within the whole uterus (4-6, 10-11).

Two or three channel applicator (Y-shaped) These applicators consist of 2 Y-shaped probes placed in 2 uterine cornua and afterloaded by Caesium. This technique leads to an adequate dose distribution in the transverse direction, whereas the dose distribution in antero-posterior direction may be suboptimal (4, 6, 8-10).

Pernot (8) umbrella technique A device of two plastic tubes fixed perpendicularly to each other at the upper end. The four arms of two loops are opened when inserted in the uterine cavity and fitted in. The applicators are manually loaded with Iridium wires.

Applicator devices with several catheters In these devices semiflexible catheters are pressed against the uterine wall. This arrangement will usually lead to an adequate dose distribution within the corpus (4, 6, 9-10).

One channel-applicator This applicator consists of one curved metallic tube of different bending with a flange indicating the length of the uterine cavity. The tube is fixed against the cervix. This applicator does not provide a sufficient dose distribution in the uterine fundus (4, 6, 9).

Uterovaginal applicators

As the target volume encompasses also the cervix and the upper part of the vagina, the typical devices for endocervical and endovaginal brachytherapy are to be used. They are usually similar to those used in treatment of cervical cancer: *Fletcher-Suit-Delclos* applicators, *Delouche* applicators, vaginal mould technique and many others designed for LDR and HDR (1, 4-5, 9, 11-12).

THE RADIOACTIVE SOURCES At present the most widely used isotopes include: Iridium-192, Caesium-137 and Cobalt-60. There have been also some pilot studies using other radionuclides, of which neutron emitting Californium-252 seems to be promising (12).

TOTAL DOSE AND FRACTIONATION Although in endometrial cancer no reference points are commonly accepted, usually ICRU Report No. 38 recommendations are used for dose specification (13). The total dose is usually delivered in 2 or 3 applications (LDR) or in several ones (HDR).

CALCULATIONS AND DOSIMETRY Target volume and reference points should be determined prior to therapy as the method of applications, the most suitable applicator and type of loading is dependent on the size of the uterus and the shape of the uterine cavity. For adequate target definition the individual anatomy of the uterine corpus and cervix, including the uterine cavity shape and uterine wall thickness are to be known. This can be properly determined only with the use of modern sectional imagine studies (sonography, computer tomography, MRI) before application.

With the computer treatment planning systems optimisation of particular case can be performed and individualised reference volume can be achieved by adequately adjusting the positions of the sources and the dwell times. The reference volume should imitate the outer surface of the uterus and the calculated doses at reference points in organs at risk should be minimalised as possible. Source positioning after application must be checked by X-rays and additionally *in vivo* dosimetry (bladder, rectum) is recommended.

RESULTS Many studies in literature have shown that radiotherapy can be effective in the management of endometrial cancer and proved that the most significant prognostic factors in endometrial carcinoma are stage and grade of disease.

In stage I endometrial cancer treated by radiotherapy alone 5- and 10-year disease free survival rates are up to 88% (5), i.e., similar to those obtained by surgery. *Perez et al.* (4) found relation between tumour stage and 5-year disease free survival rates in endometrial carcinoma treated by exclusive radiotherapy: 75-80% in stage I, 60% in stage II and 24-27% in stage III. *Rotte et al.* (10) presented 5-year survival rate of 74% in 227 patients of endometrial carcinoma in stages I-III treated by radiotherapy alone, with 79.6%, 74.3% and 33.3% in stages I, II and III, respectively. *Kupelian et al.* (14) in stages I and II found 87% and 88% 5-year survival rates but in stages III and IV results were significantly poorer (49%) with intrauterine relapse in 14% of the patients. *Grigsby et al.* (5) found in stage I patients treated by radiotherapy alone 5-year progression free survival rates of 92%, 90% and 80% for grades 1, 2 and 3, respectively. Stage II cases demonstrated a decreasing survival rate with higher grade: 53%, 63% and 38% in grades 1, 2 and 3, respectively. Decrease of survival rate with increase of tumour grade has also been demonstrated in stage III patients (50%, 33% and 25%, respectively). Incidence of locoregional recurrences observed in *Grigsby's* material was 8.7% in stage I, 34.6% in stage II and 41% in stage III. Similar results were reported by other authors. *Lehoczky et al.* (15) presented in their material of 171 patients with stage I endometrial

carcinoma 75% 5-year NED survival: 77% in G1, 68% in G2 and 53% in G3. In the series of *Taghian et al.* (16) 5-year survival rates in IA, IB and II stage were 82.1%, 64.6% and 56.2%, respectively, with grade as another significant prognostic factor. Also *Rouanet et al.* (17) in their material of 250 patients of all stages (I to III) observed 5-year survival of 65.8% with strong correlation to tumour stage and grade.

COMPLICATIONS Major complication rates reported in the literature varied from 0 to 19% (4-5, 9, 14-16) with more (about 15%) affecting the rectum and sigma than the urinary bladder (about 5%). Severe complications occurred less frequently in early-stages and the reported incidence of these complications varies from 0.7 to 3.0%. As there is an evidence of relationship between the total dose, dose distribution in the pelvis and the rate of complications (4), the careful planning may result in decreased number of severe late sequelae.

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Radiotherapy as primary therapy for endometrial carcinoma

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INTRODUCTION

THE EVOLUTION OF TREATMENT FOR ENDOMETRIAL CARCINOMA

Radiotherapy has a proud track record for helping many thousands of women from 1908, when radiotherapy was first used for uterine carcinoma, as a primary therapy. Refinements reported during the next 20 years, using an intra-uterine tube and "colpostats", established the effectiveness of radiotherapy as a treatment method. Simultaneously, surgical techniques improved, and more and more patients became operable. Soon a treatment philosophy of preoperative irradiation to the uterine and para-uterine tissues evolved. Thus, preoperative intracavitary irradiation became entrenched as therapy for all endometrial cancers for the better part of four decades (1). In the 1960's and 1970's, with the evolution of the high energy linear accelerator, the proven ability of external irradiation to eradicate cancer in the regional lymphatic structures, prompted the use of whole pelvic irradiation for patients with stage II and III endometrial cancer and for recurrent disease, supplemented by central brachytherapy. With the growth of gynaecological oncology, surgical staging became in vogue from about the 1970's, and established more refined criteria for pre- and postoperative external pelvic irradiation. Radiotherapy was reserved for high-grade cancers and infiltrating stage I cancers.

In the 1980's it became apparent that for tumours with lymphovascular invasion, clear cell (CC) and serous papillary (SP) histology, the disease may spread relatively frequently to the upper abdomen more like ovarian carcinoma and also more frequently to the paraaortic nodes. In principle then, these patients could benefit from extended field and perhaps whole abdominal irradiation, or from the irradiation of the paraaortic nodes alone, or from other types of adjuvant therapy, for example "systemic therapy" e.g. chemo-hormonal therapy. Technical advances in radiotherapy made paraaortic irradiation safer, for example by the use of three dimensionally planned "conformal therapy" with x-rays, or by irradiating with protons, where this modality is available (2).

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WHAT THEN, IS THE PLACE OF PRIMARY RADIOTHERAPY TODAY IN THE MANAGEMENT OF CARCINOMA OF THE ENDOMETRIUM?

Surgery, by means of a total hysterectomy and salpingo-oophorectomy remains the treatment of choice for stage I endometrial cancer. Radiotherapy is the only alternative treatment option for carcinoma of the endometrium in patients rendered inoperable because of medical complications, and is also indicated as palliative therapy after recurrence.

HOW EFFECTIVE IS PRIMARY RADIOTHERAPY IN ENDOMETRIAL CARCINOMA?

This modality in fact gives results comparable to that of surgery when death due to intercurrent disease is audited out. The following data and analysis will show that a disease specific survival of about 75% can be achieved for stage I disease, using techniques that may be somewhat outdated by modern standards. A few selected articles will be used to illustrate the general picture, and a table summarizing the recent literature will demonstrate survival rates that can be expected from standard radiotherapy.

Recently, *Rouanet et al.* (3) reported on 250 patients with endometrial carcinoma treated with irradiation only. The patients were treated between 1967-1986. Of these 178 had a minimal follow-up of 5 years, and 146 had a minimal follow-up of 10 years. The mean age of the patients was 68 years. *Technique:* Whole pelvis irradiation to 45 Gy with 25 MeV x-rays in 4-4.5 weeks, using two parallel opposing fields of 15x15 cm was used. Intracavitary irradiation was given with Heyman pellets from 1967-1972, using 3 to 7 pellets of 10 mg each, plus a "colpostat" placed against the cervix, giving a median dose of 3550 mg-hours. From 1972 onwards, patients were treated with a Fletcher Suit Delclos applicator with ^{137}Cesium, two insertions 10-15 days apart. This resulted in point A getting 45 Gy from external, and 30 to 40 Gy from intracavitary therapy. The total dose to point A was thus 75-85 Gy. Stage III patients received a pelvic wall boost to 55 Gy with central shielding. *Results:* At 5 years, out of 20 T1a patients, 15% died of their cancer, giving a 5-year survival rate of 85%. Of 88 T1b patients, 23% died of their cancer, giving

Table 1. Results of radiotherapy as sole treatment for endometrial carcinoma [Data modified from *Rouanet at al.* (3).]

Survival at 5 years						
Stage	No	DOD	%	DID	NED%	S-DID
T1a	20	3	15	3	70	85%
T1b	88	21	24	10	62.5	77%
T2	11	2	18		63.6	68%
T3	59	19	32.2	16	57.2	73%
Total	178	45	25.2	29	62.0	76%

DOD Died of Disease
DID Dead from Intercurrent Disease
NED No evidence of disease at 5 years.
S-DID Overall survival minus DID.

a 5-year specific survival rate of 77%. T3 patients achieved a 5-year survival rate of 68%. In toto, 16.2% died of intercurrent disease, and 25.2% of the endometrial cancer by 5 years, giving a disease specific survival of just under 75%, all stages. The data is summarized in *Table 1*. The overall survival rate (excluding deaths from intercurrent disease) at 5 years was 76.5 %, the disease free survival was 68.5%. At 10 years, the overall survival rate was 68%, the disease free survival 66%. *Complications:* Overall 11.7% but only 3.3% severe grade 3 or 4 complications, mainly observed in T3 tumours (4.5% cystitis, 2.5% vaginal stenosis and 1.5% proctitis). The causes of failure were metastases 7.3%, and local failure 24.1% (19.6% without concomitant metastases). The local control rate and the survival was related to the tumour stage and grade. **The authors conclude that radiation therapy as sole treatment is an effective modality.**

Another recent and very useful article came from the *M.D. Anderson Hospital* (4). They reviewed the results of treatment with radiotherapy alone in 152 patients with endometrial carcinoma. The preferred treatment in MD Anderson Hospital is total abdominal hysterectomy and bilateral salpingo-oophorectomy. However, between 1960 and 1986, 192 patients with medical problems were treated at MDAnderson Hospital with radiotherapy alone. Excluded were 40 patients because of superficial, in situ histology, 21 who had incomplete treatment, 7 who presented with recurrent disease, and 8 who had other primary malignancies. The remaining 152 patients were analysed. Of these 120 patients with stage I disease, and 7 with minimal stage II disease were treated with Heyman or Simon pellets or with an afterloading tandem to a mean of 6215 mg-hours, and the vagina was irradiated to an equivalent of 60 Gy. The results are summarized in *Table 2*.

In stage I disease, 10 (8.3%) were confined to the uterus. Five of these, where an attempt to salvage was made, were all successfully treated, 4 by hysterectomy and one by additional intracvitary therapy. In stage I and II patients, only 3% of tumours recurred outside of the uterus. Disease specific survival (DSS) was not significantly different if analyses by grade of tumour, but the patients with stage I and II disease and a papillary serous histology had a DSS of only 43%.

Table 2. Radiotherapy alone as treatment for endometrial carcinoma (4)

Survival at 5 and 10 years			
	No.	5y	10y
DSS (All)	152	81%	75%
Overall for 120 stage I patients	120	55%	28%
DSS for 120 stage I patients	120	87%	80%
DSS for stage II patients		88%	
DSS for stage III and IV		49%	
Uterine control rate	152	86%	83%
Late complications		4.5%	4.5%

DSS Disease specific survival

Table 3. Results of endometrial carcinoma treated with radiation alone [Modified from *Kupelian et al.* (4)]

Author	Year	Stage	No	Local recurr %	DSS %	Comp. %
Landgren	1976	HI	124	22	68	7
		IHV	26	42	22	
Abayoni	1982	HI	50	26	78	15
		IHV	16	10		
Patanaphan	1985	HI	42	14	64	2
		IHV	10	60	20	
Jones and Staut	1986	HI	146	22	61	4
		III	14	79	14	
Varia	1987	HI	73	21	43	10
Wang	1987	HI	41	22	76	5
Grigsby et al.	1987	I	69	9	88	16
Taghian et al.	1987	HI	94	6	70	17
		IIHV	10	10	27	
Lehoczky et al.	1991	I	171	20	75	0
Kupelian et al.	1993	HI	137	14	85	3
		IHV	15	32	49	
Rouanet et al.	1993	HI	119		78	11
		IHV	59	68		

DSS Disease specific survival

Lehoczky et al. (5) using Heyman pellets only, reported a local failure rate of 21 per cent. *Patanaphan et al.* (6) and *Grigsby et al.* (7) conclude that whole pelvic irradiation plus brachytherapy gives a satisfactory survival rate compared to surgery. *Taghian et al.* (8) conclude that radiotherapy alone for endometrial carcinoma gives a determinate survival rate of 72% at 5 years for stage I and II carcinoma, versus 56.6% with brachytherapy alone. *Jones and Stout* (9) have reported that 2 intracavitary insertions give better results than one: At five years, a 73% survival with two insertions versus 56% with only one insertion = significant (p< 0,015).

Rose et al. (10) did a case controlled study on 64 patients treated with primary radiotherapy. Cardiovascular disease, diabetes, age over 80 and morbid diabetes were the most frequent contraindications for surgery. Seventy five per cent of the patients completed therapy, which included both teletherapy and brachytherapy. Intercurrent disease accounted for 36% of the deaths. Clinical stage and histologic grade were significant predictors of survival (p=0.001 and p = 0.013, respectively). Ninety per cent of the patients had stage I disease. These patients were matched by clinical stage, tumour grade and time of diagnosis for patients who underwent surgery. **This case controlled study of Stage I and II patients treated by primary radiation therapy matched to surgically treated controls, showed no statistically significant difference in survival.** Dilatation and curettage with pathological examination, after completion of the radiotherapy was predictive of local control (p=0.003). The authors concluded that although surgery followed by tailored radiotherapy has become widely accepted therapy for stage I carcinoma of the endometrium, even in patients who are a poor operative risk, **the survival with primary radiotherapy is not statistically significantly different from that of surgery.**

CONCLUSIONS

1. Total abdominal hysterectomy plus bilateral salpingo-oophorectomy is the treatment of choice for early stage endometrial carcinoma.

2. Preoperative radiotherapy may confuse proper staging.

3. In inoperable patients, radiotherapy alone is a good alternative to surgery and in fact, gives results equal to that of surgery in terms of disease specific survival.

4. The 10-20% local recurrence rate with radiotherapy clearly makes hysterectomy the treatment of choice whenever the risk of operation is acceptable.

5. Although there is a significant local recurrence rate after radiotherapy, these patients can be salvaged in about 50% of cases by surgery, or even by further intracavitary radiotherapy.

6. Postoperative radiotherapy for stage I patients with recognized risk factors is a logical option which probably contributes to cure, because the survival of high risk patients treated with radiotherapy postoperatively is equal to that of patients who had surgery without risk factors (11-12).

7. Teletherapy followed by brachytherapy gives better results than brachytherapy alone.

8. Papillary serous histology had a much worse prognosis.

9. It is quite likely that the better planning, localizing and dosimetry techniques available now in radiotherapy, may further improve the results of radiotherapy. For example, some of the articles cited used parallel opposing fields. This can no longer be considered optimal therapy, and it is likely that 3D conformal techniques may help to improve results further. The flexibility of HDR afterloading techniques may likewise lead to improved results. The role of 235 Californium for intracavitary therapy is being investigated.

10. Patients who develop local recurrences after primary radiotherapy can often be salvaged by surgery.

11. Two insertions of intracavitary sources, where this forms the main source of therapy, may be better than only one insertion.

12. High dose-rate applications offer the opportunity of well fractionated techniques with tandems and vaginal cylinders. This may offer advantages over low dose-rate techniques and need to be studied.

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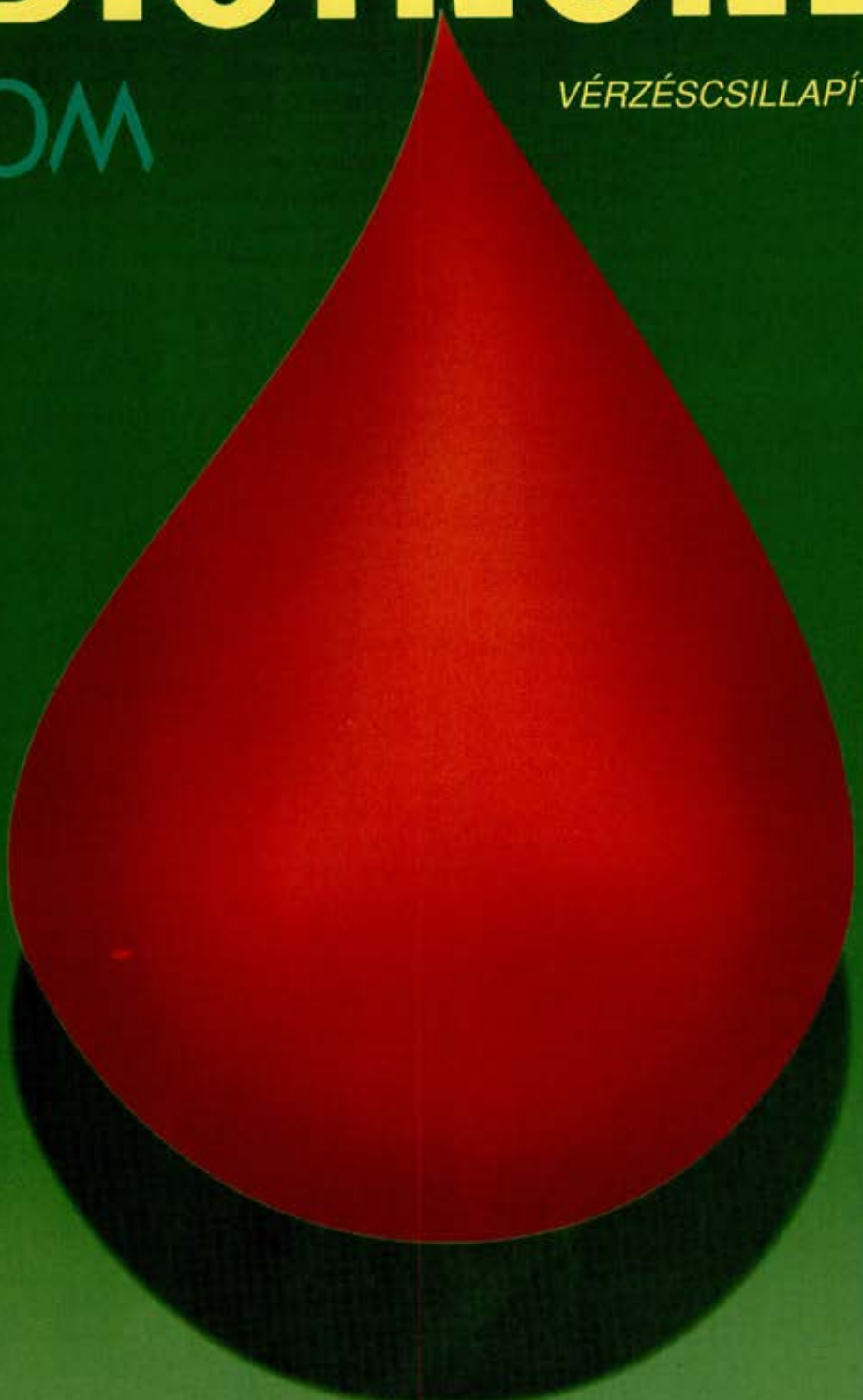

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Hatóanyag: Estraderm TTS 50: 4 mg oestradiolum kerek, lapos, átlátszó tapaszonként. Hatóanyag felszabadulás: 50 µg/nap. Estragest TTS: 10 mg oestradiolum és 30 mg norethisteronum aceticum kétrekeszes, lapos, átlátszó tapaszonként. Hatóanyag felszabadulás: 50 µg ösztradiol/nap és 0,25 mg NETA/nap. **Javallatok:** Természetes úton vagy sebészi beavatkozást követően kialakuló menopauzális ösztrogén-hiánytünetek. Postmenopausalis osteoporosis megelőzése a csonttörésekre való fokozott hajlam, ill. kockázati tényezők esetén. **Adagolás:** A kezelést az Estraderm TTS 50 tapasszal kell kezdeni, melyet hetente kétszer (3-4 naponta cserélve) kell alkalmazni. A következő két hétben hetente kétszer egy-egy Estragest TTS 0.25/50 tapaszt kell felragasztani. **Ellenjavallatok:** Emlő- vagy endomertium carcinoma, endometriosis, ismeretlen eredetű hüvelyi vérzés, súlyos máj- és vesekárosodás, Dubin-Johnson szindróma, Rotor szindróma, súlyos szívbetegség, thrombophlebitis, thrombosis vagy thromboemboliás megbetegedések, terhesség, szoptatás. **Figyelmeztetés:** Uterus leiomyomák, korábban előforduló, ösztrogén terápiával összefüggő halláskárosodás, cholelithiasis, diabetes, szívelégtelenség, hypertonia, vese- vagy májkárosodás, epilepszia, migrén, fibrocisztikus emlőbetegség, vagy a családban előforduló emlőcarcinoma esetén fokozott elővigyázatosság és rendszeres orvosi ellenőrzés szükséges. **Mellékhatások:** Bőrirritáció a tapasz alkalmazási helyén, az ösztrogén kezeléssel összefüggő reakciók, pl. emlőfeszülés, migrén. Izolált esetekben: generalizált viszketés, és exanthema, thrombophlebitis, anaphylactoid reakciók. **Megjegyzés:** + Csak vényre, "SZ" jelzéssel. **Csomagolás:** 1 doboz Estracomb TTS 4 db Estraderm TTS 50 és 4 db Estragest TTS tapaszt tartalmaz.

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Radiation therapy alone in endometrial carcinoma

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ABSTRACT Endometrial carcinoma has always been treated with primary surgery; radiation therapy is also nowadays a preoperative or postoperative approach. Recently, the role of radiation therapy as a primary treatment has achieved more importance. Radiotherapy can be performed as an external technique or a brachytherapy technique: brachytherapy is without doubt the most important approach in all stages, while external radiotherapy is usually added in advanced stages of disease. We will discuss from the technical and clinical point of view the use of radiation therapy alone in the treatment of endometrial carcinoma.

Key words: primary radiotherapy, endometrial cancer, brachytherapy.

INTRODUCTION Endometrial carcinoma is a malignant disease with an incidence which has increased in recent years, especially in developed areas, remaining still uncommon in premenopausal women: indeed the largest number of cases (75-80%) occurs after menopause, between the ages of 55 and 60. It represents almost 50% of all female genital cancers and about 10% of all malignancies in women. In Europe, the highest incidence rates are in Swiss, in Germany, in Hungary and Denmark, while lower incidences rates are in East Countries, in Britain and Sweden.

Epidemiology gave an important contribution to the discovery of the etiopathogenetic mechanisms which participate to the development of endometrial carcinoma. A relation between estrogenic therapy during menopause and endometrial carcinoma has been observed, and also obesity seems to be a factor of risk because of the high level of estrogen and the fat-rich diet. Tamoxifen therapy has been associated with an increased risk for endometrial cancer, primarily among women receiving high cumulative doses of drug (1-2).

Noteworthy is the fact that the most frequent presenting manifestation, abnormal uterine bleeding and discharge in the perimenopausal or postmenopausal woman, leads the patient to seek medical attention early in the course of the disease. The availability of a whole spectrum of office sampling techniques has made the outpatient evaluation much simpler and much less uncomfortable. As a result, the vast majority of patients are diagnosed when the disease is confined to the corpus of the uterus.

Endometrial carcinoma, if early discovered, has very encouraging survival percentages and less severe prognosis (3). Approximately three of four patients with stage I cancer will be survivors. In stage II patients the 5-year survival is not far from 60%. The good results in these cases are balanced out by the results in poor prognosis cases, which account for about 25% of patient material. There is a general agreement on considering that, in addition to clinical stage, some factors of risk are important for prognosis: list includes age (the older the patient at the time of diagnosis, the greater the chances of advanced stage), hystological type of the tumor (adenocarcinoma and adenoacantoma versus adenosquamous, papillary serous and clear cell carcinoma), differentiation (grade 3), myometrial invasion (inner one third), peritoneal cytology (found in up to 16% of all stage patients), lymph-vascular involvement, steroids receptors presence, non-tumoral endometrial characters, cancer extension in uterine cavity, nuclear grading, nucleolar grading, mytotic activity and lymph node status (4-5). With respect to this last point it has been the impression of many oncologists for years that this cancer seldom metastasizes to regional lymph nodes (6). The study of specimens removed during radical surgery revealed that this impression was wrong: the frequency of lymph node involvement has been documented to vary between 25 and 60%, according to clinical stage. Lymph nodes metastases, which also tends to be correlated with histologic grade 3 and involvement of vascular space (50% of N+ if present), have a great influence on outcome: the survival rates at 5 years were 30% for stage III and 10% for stage IV.

With regards of the stage of endometrial carcinoma, the clinical classification endorsed by the Gynecologic Oncology Group

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(FIGO) is still used for inoperable patients treated primarily with radiation therapy or when complete surgical staging is not performed: this system should be based on bimanual pelvic examination of the patient under anaesthesia as well as other diagnostic procedures than can vary with the stage of the tumor (7). Computed tomography scan (or magnetic resonance imaging) of the pelvis is strongly recommended in all patients with stage II or greater, because useful in detecting nodal enlargement, depth of myometrial invasion or extension outside corpus. Vaginal sonography has also proven to be a sensitive method for evaluating myometrial invasion. Because of the high level of operability of patients with endometrial cancer, a new pathologic FIGO staging system was introduced in 1989 in order to give a more accurate method of determining the true extent of the disease and to provide information about the need for adjuvant therapies. The value of this staging procedures for designing treatment protocols is under investigation.

GENERAL MANAGEMENT There's no doubt that surgery is nowadays the most important approach in the treatment of endometrial carcinoma, especially in early stages; for more advanced disease the management of the patients is not well standardised, with regards of the adjuvant treatment (8). Primary radiotherapy is preferred in patients with advanced age or internal problems. Because of a high proportion of patients with this cancer are obese, hypertensive and diabetic, they have often greater operative risks and in addition can demand special radiation therapy techniques to compensate for their large diameter.

In general, it is difficult to define which patients are amenable for adjuvant treatment, and also it is not sure which kind of adjuvant treatment could be useful in each case. For years patients with endometrial carcinoma in stage I who were considered at high risk for recurrence have been treated with adjuvant radiotherapy, so the integrated approach surgery-radiotherapy has been for long time the most used treatment almost everywhere. Anyway, this approach has not been demonstrated to give a sure improvement in survival rates compared to surgery. At some institutions, postoperative whole-pelvis irradiation is recommended in patients with inner one third myometrial invasion and grade 3 disease because these lesions are more aggressive and there is a much greater chance of having nodal involvement. Optimal therapy for stage II has not been clearly defined: patients at high-risk for pelvic node metastasis or local recurrences probably can be treated beneficially with adjuvant therapies, but definitive prospective radiation or chemotherapy clinical trials have not been completed. Patients with stage III disease for vaginal or parametrial extension are not good candidates for initial surgery and could be treated with preoperative irradiation. Anyway, postoperative extended irradiation is indicated for almost all patients with locally advanced disease. For more advanced lesions (stage IV) radiation therapy is often considered for long term palliation; in some cases, a persistent clinical remission of the disease can be obtained with prolonged survival (10% at 5 years). In case of recurrent carcinoma, therapy is individualised depending on the site or sites of the recurrence and may include surgery, irradiation or chemotherapy. If the recurrence is limited to the vagina or pelvis, demonstrated by laparotomy, in previously unirradiated patients high dose radiation therapy with external beam and/or implant may be considered with a fair degree of local control. For a small recurrence in the vaginal vault, the eradication of the disease can be obtained with intracavitary or interstitial implant. For large vaginal vault lesions, combined external whole-pelvis irradiation and isotope implant is the treatment of choice. Vaginal recurrences from undifferentiated adenocarcinoma usually develop more rapidly and extensively and involve the anterior vaginal wall and suburethral area, and are frequently associated with tumor spread outside the vaginal wall and into the pelvis as well as distant metastases. These lesions are usually treated with primary external whole-pelvis radiotherapy with a dose of 55-60 Gy in 6-7 weeks, followed by an implant of 20 Gy to bulk disease, if lasting local control are to be expected (9-11).

In case of extensive metastatic disease, when the patients are otherwise healthy, chemotherapy and/or hormontherapy can be proposed in addition to palliative external irradiation of metastatic sites. Drug combinations including cyclophosphamide, doxorubicin, fluorouracil and cisplatin have been tried with some success. Also Paclitaxel seems to be effective in most of cases. The likelihood of a response to hormonal therapy appears to be correlated to histologic grade and receptor status. Well-differentiated lesions are more likely to respond and are also more frequently positive for estrogen and progesterone receptors than tumors which are poorly differentiated. In a study of 114 endometrial carcinomas, the mean progesterone-binding capacity was inversely related to tumor grade (12). Moreover, lesions positive for estrogen and progesterone receptors appear more likely to respond to progestin therapy than lesions which are receptor negative. Most of the studies on the topic have been conducted with parenteral progestins. The only other agent tested in a significant number of cases is Tamoxifen, which demonstrated activity in two of three trials. At present, Tamoxifen should be considered as potentially active in endometrial tumors.

THE ROLE OF RADIATION THERAPY ALONE When surgical treatment is not indicated, because of the advanced age or general conditions of the patient, radiation therapy alone can be used both in early stages and in more advanced stages. In case of primary radiotherapy, the clinical stage of the tumor can be defined using the histopathologic report from the fractionated curettage, the measurement of the length of the uterine cavity, the findings of the clinical and radiological (CT or MRI imaging, ultrasound) examination. There is evidence from several institutions that adenocarcinoma of the corpus is relatively curable by radiation therapy alone: its response rate is similar to carcinoma of the cervix. Data coming from surgical specimen after

preoperative irradiation show a microscopic control in at least 40% of cases. Evaluation of the effectiveness of irradiation for the technically inoperable cancers is more difficult. If there is spread beyond the pelvis, there is a little chance of cure. On the contrary, when the reason for unresectability is extrauterine but still localized, there is still a chance for definitive cure. *Larson et al.* (13) from the M.D. Anderson experience reported 5-year actuarial survival rates of 67% for the 69 stage II patients receiving combined radiotherapy and surgery, of 60% for the 5 patients treated by surgery alone, and of 38% for the 9 patients treated by irradiation alone. *Berman et al.* (14) in a retrospective study of about one hundred patients with stage II carcinoma found a 5-year survival of 58.5% in case of combined approach, of 66% for patients only operated, and of 77% for patients only irradiated. Other results in the treatment of endometrial cancer by radiotherapy alone are referred on Tables 1, 2 and 3.

Low (LDR) or high dose-rate (HDR) brachytherapy treatment can represent the only therapeutic approach in patients with stage I and II disease. Total dose varies between 30 Gy with fractionated HDR brachytherapy (15) and 50-60 Gy with conventional continous LDR irradiation (16). There is a great variability among different clinicians in reference points (the points of dose prescription): "A line" at 2 cm in the lateral direction from the source axis, indicating the point on the "A line" farest away in lateral from the axis of the source, "external contour of the uterine wall", "encompassing isodose" (17-19). The patient is positioned on a gynecologic table in lithotomy position. An accurate antisepsis of the vulvovaginal region, with the lower extremities included, is performed; sterile clothes will cover the surrounding regions. A different widening of the cervical canal is needed, depending on the technique used for treatment; the dilatation needed increases with the number of catheters to be introduced (depending on the individual anatomy). Different forms of applicators can be used for treatment of endometrial carcinoma: modified Heyman packing, two or three channel applicators (Y-shaped), applicator devices with several catheters, one-channel applicators. The method of application depends on the size of the uterus and of the uterine cavity: the larger the uterus, the less suitable are rigid applicator devices. The ideal characteristics of an intrauterine applicator should be the following ones (20):

- the applicator should have a diameter less than 10 mm (to be easily inserted);
- there should be a sufficient number of intrauterine probes available;
- the probes should have a contact with the inside of the uterus (with the tumor), and should lie laterally to the tube edges to be able to deliver a high dose;
- the probes should be flexible enough to conform to the inside of the uterus and the tumor;
- the probes should be geometrically stable not to change position during the treatment and for the reproducibility of the treatment planning;
- reduction of the risk of uterine perforation (adequate probe's shape);
- the applicator must be easy to insert and to remove;
- the applicator should have standard loading plans for different sizes of uteral lumina and should also provide individual variability.

Table 1. Treatment outcome of stage I disease for carcinoma of the endometrium: radiation therapy alone (24).

Stage I	No. Patients	Survival % 5-year	Recurr.pelvis		Rec.pelvis+ dist.metast.	Distant metastases
Grigsby et al.	69	88.1	0		6 (8.7)	3 (4.3)
Landgren et al.	45 (IA)	75	4 (8.9)		3 (6.7)	5 (11.1)
	41 (IB)	80	10 (24.4)		3 (7.3)	3 (7.3)
Salazar et al.	25		6 (24)			8 (32)
Spanos et al.	30 (IA)			5 (16.7)		Not reported
	27 (IB)			11 (40.7)		
TOTAL	180		20 (18)		12 (6.7)	19 (10.6)

Table 2. Treatment outcome of stage II disease for carcinoma of the endometrium: radiation therapy alone (24).

Stage II	No. Patients	Survival % 5-year	Rec.pelvis	Vagina+ Pelvis	Pelvis+ dist. metas	Distant metastas.
Grigsby et al.	26	53	2 (8)		7 (27)	3 (12)
Landgren et al.	38	65	3 (7.9)		4 (10.5)	9 (23.7)
Salazar et al.	8		3 (37.5)			2 (25)
Spanos et al.	21			4 (19)		Not reported
TOTAL	72		8 (11.1)		1 (15.3)	14 (19.4)

In case of superficial carcinoma a dose encompassing the mucosa and submucosa may be sufficient; in case of infiltration of the myometrium the whole uterine wall must be included. At present it is not easy to discriminate myometrial infiltration without histopathologic examination of the uterus surgically removed: for this reason, the whole uterine wall must be treated in any case. It is really very important to define the exact anatomy of the patient before performing the treatment, to obtain a direct relation of the distribution of tubes and anatomy. With this purpose sectional imaging can be performed before the application, such as echography and computed tomography (21). As a supplement for intrauterine brachytherapy, endocervical and endovaginal brachytherapy can be performed, to give an adequate treatment also to the adjacent areas of the uterine corpus (cervix, upper vagina). The reason is that it is necessary to prevent recurrence and metastases in these structures (22). From the technical point of view, the treatment to cervix and vagina must be decided depending on the technique and the target of the treatment to endometrium. To treat the cervix, devices for endocervical brachytherapy can be useful, with an additional treatment also to the upper part of the vagina. If the therapeutical decision is to treat only the upper vagina, applicators can be the same used for postoperative brachytherapy of the vaginal cuff (21).

In patients with high-risk stage I or II disease, the intracavitary treatment should be added to external irradiation. There is no difference in the intracavitary total dose between brachytherapy alone and brachytherapy combined with external pelvic radiotherapy. The aim of external beam irradiation is to give a supplement of the dose (from 25 to 50 Gy) to the parametrial tissue and lateral pelvic lymph nodes. When an additional external pelvic radiotherapy with open fields is needed, the brachytherapy volume must be excluded at least after 25 Gy, inserting a midline 5HVL (half value layer) block into the anterior and posterior opposed fields to shield the central area that has received high dose treatment from brachytherapy. For adequate brachytherapy, in case of combined treatment brachytherapy/teletherapy, there are two major requirements:

- a dose distribution adapted to the individual situation, with concentration of dose in the target volume and with dose sparing in the organ at risk;
- a practical technique with regard to radiation protection and to reproducibility of source positioning.

External pelvic irradiation (from 50 to 60 Gy) is the treatment of choice for patients in stage III or IV. To ensure a high central pelvic dose the treatment can be individualized with one or two intracavitary insertions or with interstitial implantation, depending on the sites of bulk tumor. External beam irradiation of the pelvis directs treatment to the primary tumor as well as to sites of local extension and potential lymphatic spread (21). Treatment planning is performed with the aid of a simulator reproducing the geometry of the treatment machine, but allowing fluoroscopic visualization of critical structures, and radiography of diagnostic quality. Treatment should be directed to sites of known tumor extension with a margin of normal tissue, and may involve prophylactic irradiation of sites of potential subclinical nodal involvement. The tolerance of surrounding tissue must be appreciated and all efforts made to reduce the late complications to these tissues by limiting the radiation dose that they receive.

Table 3. Treatment outcome of stage III disease for carcinoma of the endometrium: radiation therapy alone (25).

Author	No. Patients surviving 5 years after irradiation only (stage III)	
Lampe (1963)	12/50	(24%)
Kottmeier (1959)	17/62	(27.4%)
Landgren (1976)	6/26	(26%)
TOTAL	35/138	(25.4%)

The pelvic structures to be included in the treatment volume usually include the uterus, cervix, a variable length of vagina, and regional lymph nodes. Paraaortic field radiation has a significant complication rate and should be reserved for patients with radiological evidence of lymph node metastases. The superior margin of the pelvic fields extends to L4-L5 if the common iliac nodes are to be included. The inferior margin is determined by the length of vagina to be included and should give at least a 3-4 cm margin on the cervix or the most distal point of vaginal tumor extension. A radiopaque clip or marker is placed at the vaginal apex or cervical os, and under fluoroscopic visualization the inferior field margin is determined. Lateral film boundaries include a 1-2 cm margin at the widest portion of the bony pelvic inlet on anteroposterior (AP) and posteroanterior (PA) projection. When lateral pelvic fields are employed, the superior and inferior borders are the same as those used for the anterior and posterior fields. Rectal contrast material is inserted for simulation of the lateral fields, and the posterior field edge should bisect the rectum in order to include the cervix, vagina, internal iliac and presacral nodes. The anterior field edge extends 1-2 cm anterior to the pubic symphysis for inclusion of the external iliac lymph nodes. Oral contrast can be useful for visualization of the small bowel within the pelvis during simulation. Bladder contrast, with distension, may be employed in an attempt to push loops of small bowel out of the treatment field. Ideal treatment employs megavoltage (from 10 to 25 MeV) photon beams.

COMPLICATIONS OF THERAPY Surgical, radiotherapeutic or combined treatment by surgery and adjuvant irradiation of endometrial carcinoma is quite well tolerated. Grade 1 complications are minor and self-limiting, responding to outpatients management. Grade 2 complications are often recurrent and may require hospitalization, but respond to medical management. Most serious, life threatening Grade 3 complication requiring surgical intervention, rarely occur with adequate technique. Major complications with a preoperative implant and hysterectomy occurred in 1% of 199 patients in a study from *Stokes and colleagues* (26). However, if the intracavitary insertion was given postoperatively, 12% patients (3 of 26) had signifi-

cant complications. With adjuvant external whole-pelvis irradiation, the complication rate was 2% (5 of 264) but increased to 18% (7 of 40) if the whole-pelvis dose exceeded 30 Gy. Eight major gastrointestinal and four urinary complications occurred in 304 patients, and the most frequent complications were bowel obstruction, ureterovaginal fistula, urethral stricture, haemorrhagic cystitis and rectal ulcer. In general, the most frequent major complications of radiation therapy of endometrial malignancies involve damage to the bladder and bowel (23).

In addition to the impact of total dose, which is really a main topic in complication's discussion, techniques used in the delivery of radiation therapy also have an impact on complications. Complications from external beam therapy relate to beam energy, volume irradiated and daily fractionation. High energy beams offer optimal dose distribution to deep pelvic tissues. AP/PA techniques employing low energy beams are to be avoided. In designing external beam treatments, shaped fields will allow exclusion of considerable normal tissue, thereby decreasing the potential for late tissue damage. Small bowel contrast can help determine bowel position and motility and allow field or dose modification to avoid toxicity (27). Some techniques to push small bowel loops out of the pelvis have been described and include bladder distension and treatment in the prone position with upward external pelvic pressure or a "false tabletop" for anterior displacement of the bowel (28). Complication rate is also directly related to the volume of tissue irradiated. Extended field treatment is adopted to include the paraaortic lymph nodes either prophylactically or therapeutically. Multiple field techniques and doses of 45-50 Gy have been advocated (29). The severity of complications appear to increase when doses over 45 Gy are employed to boost gross disease.

Intracavitary applications may contribute to the development of late complications if careful attention is not paid to the applicator geometry, isotope loading, and bladder and rectal doses. The type of applicator employed is important to the development of late tissue damage. Use of rigid Ernst applicator has been related to excessive vaginal fistula formation (30). When patient anatomy is less than ideal, as with a small, atrophied or scarred vagina or with bulky tumor at the vaginal apex, bladder and rectal doses are increased; this occurs because of downward displacement of the applicator system or poor lateral separation of the vaginal sources.

Various high-risk not-treatment related factors are associated with an increased risk of late radiation complications, and when present may warrant a planned reduction in total dose. Advanced age, hypertension, anemia, poor nutritional status, diabetes mellitus and obesity have all been correlated with increased complications and poor outcome. A history of previous abdominal or pelvic surgery or of pelvic inflammatory disease, colitis or diverticulitis is likewise associated with an increase of complications (31).

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Current status of preoperative and adjuvant radiation therapy in cervical carcinoma

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The conventional treatment of patients with stage Ib and IIa cervical carcinoma consists of either radical hysterectomy and bilateral pelvic lymphadenectomy or radiation therapy combining the whole pelvic external irradiation with local brachyradiotherapy. These treatment modalities are recognized as equally efficacious with respect to local control and survival.

However, in younger patients surgery is often preferred to radiotherapy, because after irradiation ovarian function is eliminated and sexual function is often compromised. In addition, late complications of radiation are avoided. Further, it is necessary to choose the type of treatment depending on the patient's condition, the skill and ability as well as the technical conditions of the team for either method of treatment.

Operative treatment has been the treatment of choice in stages IB, IIA and early IIB of cervical carcinoma at the Department of Obstetrics and Gynecology in Ljubljana for decades. Our experience in this field is based on over 3000 cases treated by Wertheim operation and goes back to the year 1907 when the first Wertheim operation in Ljubljana was performed. In spite of the fact that our principal method of treatment has been the surgical one, we have been of the opinion that in high risk cases with bad prognostic factors the operative treatment should be combined with radiation. At least four major prognostic factors have been identified:

1) Size and extent of the primary tumor
2) Tumor grade
3) Lymph – vascular space invasion
4) Presence of lymph node metastases

Of these four variables, nodal metastases appear to be the most important prognostic indicator with the remaining factors influencing survival mainly as a reflection of the risk of nodal spread.

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Preoperative brachyradiotherapy and/or external irradiation has been applied in cases of large exophytic tumors in order to reduce tumor size, making the operation easier and in hope to avoid the central recurrence following radical hysterectomy. Adjuvant postoperative whole pelvic irradiation, based on pathohistological examination of the surgical specimen, has been applied to improve pelvic control and presumably survival in patients at increased risk of recurrence following radical hysterectomy and pelvic node dissection. It has been believed that microscopic extracervical metastases could be treated with external irradiation.

At our Department over the last 25 years the number of cases treated with preoperative irradiation for big size tumors has diminished, but postoperative adjuvant radiotherapy is still applied in stages IB or IIA of cervical carcinoma when these adverse factors are present: positive lymph nodes, close or involved surgical margins, deep stromal invasion (more than half of cervical depth), exophytic lesions greater than 3 cm in diameter, or microscopic parametrial involvement. Surgical procedure consists of Wertheim-Meigs-Novak radical hysterectomy (Piver III) with pelvic lymphadenectomy.

The 5-year survival of patients with cervical carcinoma stage Ib treated in two different periods (1965-72 and 1978-87) is shown in *Table 1*. (1, 2).

Table 1. Cervical carcinoma stage IB: 5-year survival

Period	No	Surgery + irradiation	Survival No	%
1965-72	259	38%	192	74
1978-87	248	54%	192	77

Of the 259 operations (1965-72) there were 49 cases (19%), and of the 248 operations (1978-87) there were 7 cases (3%) of Schauta-Amreich procedure, all other operations were Wertheim. In the period 1965-72 Wertheim operation was combined with irradiation in 38% of cases, and in the period 1978-87 in 54% of cases. Preoperative brachyradiotherapy consisted of one application of 4000 cGy to point A (in the first period radium

according to Manchester scheme, and in the second cesium with afterloading technique). Postoperative external radiation was delivered to the pelvis at a dose of 5000-5600 cGy in 4 weeks. The difference in the 5-year survival between the two periods is not significant, although in the second period significantly more patients were submitted to the combined treatment (15% preoperative, 34% postoperative, and 5% pre- and postoperative irradiation). The percentage of positive lymph nodes was about the same in the two compared periods (18%). Irrespective of postoperative irradiation, the overall survival in these cases was 56%, whereas in cases of three or more positive pelvic nodes it was only 18%.

In women younger than 35 years the share of cervical carcinoma related to the total number of cases increased from 4.9% in 1965 to 17% in 1989 (3). The number of cases of cervical adenocarcinoma has raised from 6 to 22% of the total cervical carcinoma cases in the last 15 years. Younger age and the histologic type of cervical carcinoma have not changed our treatment policy substantially, and the 5-year survival is comparable with that of older patients and squamous type carcinomas.

Our analysis (4) on 174 Wertheim and 29 Schauta operations demonstrated that severe urological complications were significantly more frequent in cases undergoing combined treatment. No case of permanent hydronephrosis was observed in only surgery group. However, permanent hydronephrosis requiring surgical treatment was observed in 8.3% of preoperatively irradiated cases, in 8% of postoperatively and in 12% of pre- and postoperatively irradiated cases. The percentage of ureterovaginal fistulas was 2.5%, irrespective of radiation therapy. We have no evidence of major gastrointestinal complications.

The question remains whether pre- and/or postoperative pelvic radiotherapy improves survival. Morrow et al (5) presented a retrospective series with a review of the literature and he could not identify a significantly improved survival in patients with positive lymph nodes who received postoperative irradiation. Postoperative radiotherapy may control local pelvic disease, but does not improve the overall survival, because more than 60% of recurrences were outside the radiation field (5-7). Other authors (8-10) suggest that adjuvant radiotherapy after radical hysterectomy produces favorable survival results with limited morbidity, especially in high risk cases with only one or two adverse factors. According to the published data (8-9) the major morbidity after combined therapy is genitourinary and gastrointestinal, and varies from 3 to 30%. In our analysis severe complications after combined treatment were mainly urological (from 8 to 12%).

Our data demonstrate that in patients with positive nodes, especially in cases with three or more positive nodes, the prognosis is significantly worse, and the overall 5-year survival was about 55-60%, irrespective of the combined surgical-radiation therapy.

In conclusion, there remains the unresolved problem of the efficacy of adjuvant pelvic radiotherapy in cervical carcinoma. Because in patients treated with combined therapy recurrences are mainly distant, not only adjuvant regional radiotherapy, but also systemic chemotherapy should be considered in cases at high risk for subclinical metastatic disease, especially because there has been little improvement in survival in cervical carcinoma in the past decades.

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Current status of pre-operative and adjuvant radiotherapy in carcinoma of the cervix

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INTRODUCTION In early stage carcinoma of the cervix radiotherapy and surgery can produce similar survival rates. However, there is still a significant number of patients who relapse following uni-modality therapy, making combined treatment an attractive possibility.

Radiotherapy adjuvant to surgery may be by external beam or intracavitary irradiation or a combination of the two. It may be used as a planned procedure either prior to surgery or after surgery has been completed. However, its use may also be unplanned but dictated by unexpected findings at surgery, for instance when extensive nodal disease is found at radical hysterectomy or when an incidental invasive carcinoma of the cervix is found histologically after simple hysterectomy.

RADICAL RADIOTHERAPY PRIOR TO NON-RADICAL SURGERY This combination of treatment would appear to offer the possibility of removing residual central disease that has not been erradicated by radical radiotherapy. However, the results of this combination for non-bulky tumours are disappointing as even the addition of simple hysterectomy to radical radiotherapy greatly increases the complication rate and yet the survival rate is not improved. This is because the finding of residual disease in the uterus after radical radiotherapy is an indicator of likely distant spread and these patients die of metastases (1). Those without residual disease undergo surgery unnecessarily.

For bulky tumours the combination has shown a decrease in pelvic recurrence rate in some series (2) but no increase in survival (3-4). In addition not all series have even shown the decrease in pelvic recurrence rate (5). Nevertheless, an increase in the severe late complication rate is almost universal in these reported series and can be as high as 16% (5). The addition of chemotherapy to this regimen also offers no advantage to the patient (6).

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In conclusion it would appear that a routine policy of radical radiotherapy followed by hysterectomy is not justified on the basis of improving survival in either non-bulky or bulky disease. The combination of therapies increases the complication rate and should be reserved for those patients who are shown to have definite residual disease after radiotherapy. This assessment should probably be made at least three months after the completion of primary radiotherapy by which time radiation-damaged malignant cells should no longer cause difficulty with the cytological and histological diagnosis of residual disease.

NON-RADICAL RADIOTHERAPY PRIOR TO RADICAL SURGERY This approach has been advocated to 'debulk' tumours and to make surgery technically easier. No reports exist showing a survival advantage, in comparison with a control group of patients, to the addition of non-radical radiotherapy prior to radical surgery when compared to radical radiotherapy alone or radical surgery alone (7). However this approach is advocated by some workers on the basis of uncontrolled trials (8). In addition, the late complication rate is again higher than when either modality is used singly and the complications seen may be of higher grade. This increase in the complication rate may not be as severe when the preoperative therapy is intracavitary brachytherapy alone rather than external beam irradiation with or without brachytherapy. Nevertheless in the absence of a survival advantage any increase in the complication rate must argue against this combination of therapies.

RADIOTHERAPY AFTER RADICAL SURGERY The routine use of post-operative radiotherapy seems not to be justified (9) and if it is to be used then a group of patients to whom it may be of benefit needs to be defined by poor-prognostic indicators found at surgery. Over the years these have been identified as narrow or involved margins of excision, deep cervical stromal invasion, involvement of the parametria, lymphovascular space invasion and the presence of pelvic lymph node metastases *(Table 1.)* (10). Whilst it would be hard to argue against the logic of giving post-operative radiotherapy when there is known residual disease, as when there are known involved margins of excision or unresected malignant lymph nodes,

there is no universal agreement that any of the other poor prognostic factors defines a group that are benefitted by post-operative radiotherapy.

The most-studied poor prognostic factor is lymph node positivity. *Eisner et al.* (11) in a small series of patients showed no advantage to post-opertive radiotherapy if fewer than three pelvic nodes were involved. In a study conducted retrospectively by *Kinney et al.* (12) no improvement in disease-free survival could be identified between node-positive patients who did or did not receive post-operative radiotherapy, when matched for tumour stage, size and number and location of nodal metastases, although the pelvic recurrence rate was reduced. Nevertheless, many radiotherapists would consider this reduction in pelvic recurrence rate to be worthwhile and post-operative radiotherapy is given to node-positive patients in many centres (13).

Table 1. Prognostic factors for patients with carcinoma of the the cervix found to be significant on univariate analysis.

Substage
Tumour size
Depth of invasion
Histological type (small cell, adenoid cystic)
Tumour differentiation
Lymphatic invasion
Vascular invasion
Lymph node involvement
Number of nodes involved
Parametrial invasion
Pregnancy at diagnosis
Incomplete surgical margins

From: *Logue and Hunter* (13)

Table 2. Algorithm for the post-operative treatment of patients with cervical carcinoma

	All stage IB/IIA	
>3 positive nodes	nodes negative	
Extrapelvic and pelvic relapse risk	Unfavourable constellations of T-factors	T-factors not unfavourable
	Mainly pelvic relapse risk	Low relapse risk
Pelvic and systemic treatment	Pelvic radiotherapy	No further treatment

From: *Thomas and Dembo* (14)

Thomas et al. [14] used the available data to produce an algorithm for the post-operative treatment of patients with cervical carcinoma *(Table 2.)*. Unfavourable factors, in addition to nodal positivity, were identified as large tumour size, deep stromal invasion, lymphovascular space invasion and poor tumour differentiation *(Table 1.)*. Although adenocarcinoma anecdotally has a worse prognosis than squamous carcinoma there is no evidence that this should be taken as a separate poor prognostic feature when considering the use of post-operative radiotherapy.

DEBULKING OF PELVIC LYMPH NODES AND RADICAL RADIOTHERAPY *Hacker et al.* (15) report that in contrast to simple hysterectomy, pelvic node debulking without hysterectomy in patients with known nodal metastases, prior to radical radiotherapy, may prolong disease-free survival.

However, there is no evidence that reversing the order of treatments and carrying out a lymphadenectomy after radical radiotherapy adds anything to survival, although this is a poorly-studied area.

INTRA-OPERATIVE RADIOTHERAPY This is very much an area of research. Intra-operative irradiation of the pelvic side wall by remote loading high dose-rate brachytherapy, when there is residual disease, may offer the opportunity to deliver a high dose to disease whilst sparing bowel. This may be packed away from the irradiated area during treatment and receive less dose than is possible with external beam treatment or irradiation of the pelvic side wall by afterloaded brachytherapy tubes delivered post-operatively.

PROPHYLACTIC PARA-AORTIC IRRADIATION Prophylactic irradiation of the para-aortic nodes is associated with marked morbidity. As a result this treatment has probably received a more critical review than the relatively well-tolerated adjuvant pelvic radiotherapy. In a review of the EORTC study of randomised para-aortic node irradiation by *Haie et al.* (16) it was concluded that, on the basis of randomised controlled clinical trials, there was no justification for this treatment.

RADIOTHERAPY AFTER SURGERY FOR INCIDENTALLY-FOUND TUMOURS It is uncommon for advanced cervical carcinoma to be found incidentally and the usual circumstance is for an invasive carcinoma to be found in the endocervical canal following hysterectomy for cervical intra-epithelial neoplasia. Patients with stage Ia1 tumours probably need no further treatment as the incidence of nodal disease or of vaginal vault recurrence is very low. However, patients with more advanced stages of disease should receive both pelvic radiotherapy and vaginal vault brachytherapy. Typically 45Gy in 25 fractions over five weeks followed by a brachytherapy insertion at either low or high dose-rate to deliver the equivalent of 15Gy at 0.5cm depth, is well tolerated. With a policy such as this the survival of patients with completely resected stage I tumours

can be as good as those treated with radical surgery or radical radiotherapy (17). Patients with incompletely resected disease fare badly as the opportunity to boost central disease by brachytherapy is lost when an intracavitary insertion cannot be completed.

CONCLUSIONS The role of radiotherapy as an adjuvant to surgery is not well explored in randomised controlled clinical trials. Its use has varied between pre-operative and post-operative therapy and has been dictated by a number of prognostic factors. Whilst pre-operative therapy can be said probably to be worthless, post operative therapy, dictated by an algorithm of risk factors, may benefit the patient both in terms of disease-free survival but also in reducing the pelvic recurrence rate and the symptoms associated with that.

Prophylactic irradiation of the pelvis of all patients post-operatively is not indicated and nor is para-aortic node irradiation.

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Radiation therapy versus surgery in early stage cervical cancer – a historical perspective

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ABSTRACT The author summarises the almost one century history of the operative and radiation therapy of cervical cancer, paying tribute to the memory of the most important authors who contributed to the development and improvment of radiation therapy or radical hysterectomy techniques listing the periods of discreditation and resurgence or different combinations of both methods.

Key words Wertheim hysterectomy, cervical cancer, radiotherapy

Until the last decades of the nineteenth century no distinction was made between the cancer of the cervix or the corpus of the uterus. The cancerous uterus was first surgically removed by *Wrisberg and Osiander* at the end of the eighteenth century. The generally accepted name of the radical hysterectomy is the "Wertheim operation" or a combination of names, including the name of one of the authors who contributed to the modification of the method: *"Wertheim-Latzko"*, *"Wertheim-Meigs"*, *"Wertheim-Okabayasi"*. But the idea of "radical" hysterectomy, the removal of the potentially infiltrated parametria together with the uterus, was not *Wertheim's* idea. The firtst radical abdominal hysterectomy was performed in 1878 by *W. A. Freund* in Breslau. *Freund* performed 66 extended hysterectomies, but the perioperative mortality rate was 72 %. Before *Ernst Wertheim*, other surgeons, *Ries, Clark* and *Rumpf* accepted also *Freund's* concepts, and performed radical abdominal interventions. It was *E. Ries*, one of *Freund's* students, who in 1895 first performed pelvic lymphadenectomy in conjunction with the radical removal of the uterus. All three authors published their methods, but none of them was aware of the work of the others. *Wertheim* in his historical work, "Die erweiterte abdominale Operation bei Carcinoma colli uteri", published in 1911, mentions the name of these predecessors.

It was *Ernst Wertheim*, who devoted his carreer to the develepment of the operation, and acquiring a vast experience, first formulated the scientific bases of the intervention. *Wertheim* also popularized the method in an impressive number of publications, so justly the intervention soon became known as the *"Wertheim operation"*.

Ernst Wertheim was born in 1864 in Graz. He was first the assistant of *Rudolf Chrobak* and after it of *Friedrich Schauta*. He performed the first radical abdominal hysterectomy in 1898. Between 1910 and 1920 was the chief of the II. Universitaets-Frauenklinik, a position he filled with the greatest distinction until his death in 1920. When he published his first monography about the radical histerectomy in 1911, mentioned above, he had the experience of 500 cases, and not a single patient was lost for follow-up.

The description of the operation was based on impressive scientific work. In eighty cases he carried out the histological study of the parametrium and lymph nodes, examining the prodigious total of 40 000 serial sections. The pathological findings convinced *Wertheim* about the legimitate of his procedure. In the monography already mentioned he wrote: "The correctness of our procedure was proved to us by histological examination of the extirpated organs. These showed the teaching to be false that cervical cancer transgresses the bounds of the uterus, only late, for in a considerable number of apparently early cases the carcinoma had sent his offshoots and advance guards to the parametrium and regional lymph nodes. This had not been shown previously by histological examinations of this sort." He also emphasized the impotance of exploratory laparotomy character of the intervention: "Since it is impossible to determine the extent of spread of the dissease by examination, one must consider every operation for carcinoma of the uterus as an exploratory laparotomy. Only after the abdomen is opened it is possible to say whether the operation can be completed or not. Laparotomy provides the opportunity of seeing the condition of the lymph nodes, the ureters, the blader and the rectum. The eye can see, the fingers can palpate, and if this is not enough, the peritoneum can be opened up without the operation losing its exploratory character." Systemic lymphadenectomy was added to the procedure by *Latzko and Schiffmann* (1919).

Radium was discovered in 1898 by *Marie* and *Pierre Curie*. The radiotherapy began in 1901 when *Pierre Curie* loaned *Dr. Danlos* a small quantity of radium, who made surface applications for the

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treatment of skin lesions. In 1904 *Freund* already used radium in gynaecological treatment. He cured vulvar lesions with superficial radium applications. Intracavitary therapy started in 1905 when *Dr Robert Abbe* in New York treated fibromyoma of the uterus with radium. As soon as radiotherapy was introduced in the treatment of cervical cancer, the dispute had started between those who advocated surgery and those who advocated radiotherapy. This dispute still continues in the 1990s. At the end of the second decade of this century radiotherapy was generally held superior to surgery in the management of cervical cancer. *Döderlein* who was a good friend of *Ernst Wertheim* wrote to him ironically in this period, that he is already a historical personality and that his operation will never be performed in the future.

The early arguments were encapsulated in an article by *Heymann:* "Radiological treatment of uterine cancer versus surgical intervention" *(Heymann 1925).* This article stated that radiological therapy carried out was greatly superior to surgical intervention. The recurrence rate was only 20%, and the complication rate was significantly lower. In this period the important brachytherapy schools were formed, in Stockholm at the Radium Hemmett Hospital *Heymann and others* treated cervical cancer with three radium applications of 24 hours at 1 week intervals. In Paris *Regaud* concluded that a prolonged treatment using low intensity radium tubes was more effective than shorter applications with higher intensity tubes. In Manchester *Paterson and Parker* designed the intersticial source distribution rules, still used today. In New York *Quimby* also studied the radiation dose distributions of radium packs and prepared dosimetry tables for individual sources. The radiation side effects were also recognised in this period, the *"Becquerel burn"* (he carried radium tube in his waistcoat pocket), and aplastic anaemia were both observed.

The renaissance of the Wertheim operation took place in the United Sates in the 1940s, and was due to the personality, immense scientific work and numerous publications of *Joe V. Meigs.* After two decades of radiotherapy he recognized its limits. The results did not improve in time and the complication rate, especially the late complications, was high. In early cervical cancer he obtained a 75% five year survival rate with his modified *Wertheim operation.* In 1944 at the Fifty-Sixth Annual Meeting of the American Association of Obstetricians and Abdominal Surgeons he summarised his arguments in favour of the surgical treatment:

"1. If the cervix has been removed, there is no chance for a recurrence in it.

2. If the cervix has been removed, no cervical cancer can regrow in it as a recurrence.

3. Certain cancers of the cervix are radiation resistant, a fact proved at the Pondville Hospital, where multiple biopsies are performed at the time the X-ray and radium treatment are being carried out.

4. There will be less damage to the bowel if surgery is undertaken. Lately, forty-six cases of serious bowel injury have been found in our clinics.

5. From the work of *Boney and Taussig* it is obvious that patients with lymph node metastases can be cured by surgery in some instances, and these authors belive that it is not possible to cure with radiation cancer in lymph nodes deep in the pelvis."

From the renaissance period of the Wertheim operation we also have to mention the name of *Taussig* and *A. Brunschwig, S. Way, Okabaiasi, M. Dargent* and *A. Tailhefer.*

During the 1950s and 1960s, in the atomic age, new radioisotopes were developed and used as sources, and afterloading methods were developed to protect physicians performing brachytherapy. The introduction of Co teletherapy and medical linear accelerators for electron-beam treatment diminished the popularity of brachytherapy in the 1960s and 1970s. In the 1980s there was a renewed interest in all forms of brachytherapy in conjunction with other modalities.

Meigs and *Brunschwig* never combined radiotherapy and surgical treatment. The idea of the combined treatment became pupular only about 3 decades ago, altough it was described by *Monod* and *Dannrenther* in 1922 and 1924 respectively. *Taussig* suggested adjuvant lymphadenectomy after irradiation. The combination of surgical treatment and irradiation is still popular in many centers, although the experince of other centers showed that the results did not improve significantly while the side effects of the two treatment modalities summarise.

Albert Döderlein was only partially right, *Wertheim* entered the history, but his operation is still performed after a century, and the dispute that began in the 1920s between the partisans of surgical or radiation treatment of the early cervical cancer still continues.

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Radiation therapy versus surgery for early stage carcinoma of the cervix

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INTRODUCTION Radiotherapy used to be the mainstay for the treatment of all stages of cervical carcinoma till the emergence of better surgical, anaesthetic and antiseptic techniques. The relatively recent development of gynecological oncology as a subspecialty, gave a further impetus to better defined and more widely used, surgical management. Excluding *in situ* lesions, whether to use surgery for stage IB to IIA lesions, or radiotherapy, remains a topic of debate (1). However, since both modalities are very effective for early disease, both modalities have their place, and are in fact complementary.

Zola et al. (1) critised the very small number of randomised trials to address the issue of radiotherapy versus surgery. They point out that only four randomised trials on this question were ever done, stating as a reason that most clinicians are so strongly in favour of one of the two alternatives, that it is almost impossible to set up a randomised trial! In our experience, this is not so at all, and the excellent co-operation between radiotherapist and surgical colleagues in gynecology, at least in our institution, simply means that we are mutually aware of the benefits of both modalities, and there is no enmity. The correct clinical assessment at the time of presentation allows an individualisation of treatment of all early stage tumours so that either radiotherapy, surgery, or a combination of both may be used in the treatment of this disease.

SELECTION OF PATIENTS FOR SURGERY Surgery is contraindicated for lesions larger than IIA, from which point radiotherapy becomes the dominant treatment modality. Lesion size may have a bearing on management of stage I-II lesions (2).

Surgery and radiotherapy both offer some advantages (and disadvantages), and these should be discussed with the patient. The complementary role of the two modalities should be explained to the patient ab initio, to facilitate the later management of possible recurrences or complications. *Stock et al.* (3) showed that postoperative pelvic irradiation for patients with recognized risk factors, improved pelvic control significantly. This was evidenced by a 5-year actuarial pelvic control rate of 78% vs 45 %.

SOME FACTORS FOR CONSIDERATION *VIS A VIS* SURGERY *Time* which the patient can invest for treatment (radiotherapy needs a daily dose for 6 weeks). The *psychological perceptions* of the patient. Some patients feel more comfortable with surgery and the tumour "removed". Better *functionality of the vagina* is the accepted outcome with surgery. This is especially important to younger patients. The *ovaries can be preserved* in selected, younger patients. The *complications* with surgery are mainly acute in nature, with few long term sequelae, whereas with radiotherapy the sequelae are mainly late.

Surgery may be the treatment of choice if good radiotherapy is not practised in the particular environment.

SELECTION OF PATIENTS FOR RADIOTHERAPY Radiotherapy (RT) has advantages: RT is the only successful alternative therapy for patients with medical contraindications to surgery. Radiotherapy offers equal disease specific survival to surgery *(Table 1.)* (9-10). This is a very fortunate situation for patients, and doctors alike.

RT may be indicated as an adjunct to surgery, e.g. for barrel shaped lesions. Studies by *Gallion et al.* (2), *Stock et al.* (3), *Potish et al.* (4) suggest a lower recurrence rate in patients treated with a combined approach. *Berek et al.* (5) advocate radiotherapy, before a standard extrafascial hysterectomy for bulky lesions, i.e. barrel-shaped, or in general, lesions larger than 4 cm in diameter. *Heller et al.* (6) showed that postoperative radiotherapy after total pelvic lymphadenectomy in the presence of positive nodes, followed by radiotherapy, improved the 5-year survival rate from 45% without radiotherapy to 71% with radiotherapy. *Rotman et al.* (7) reported a

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Table 1. Comparative survival rates for patients with stage I carcinoma of the cervix treated by radiotherapy (RT) or surgery (S)

RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY FOR IB, ACTUARIAL SURVIVAL RATES

Author	Pt No	Type	5-year survival %
Ketcham	28	actuarial	86 (S)
Park	126	actuarial	91 (S)

RADICAL RADIOTHERAPY RESULTS, ACTUARIAL SURVIVAL RATES

Mallinckrod Inst	374	actuarial	85 (RT)
Hanks PCS Selected Facilities		actuarial	92 (RT)
Fletcher	549	actuarial	91.5 (RT)
Perez Radiotherapy	312	actuarial	87 (RT)

ABSOLUTE SURVIVAL RATES STAGE IB

Author	Pt. No	Survivors	%
Liu and Meigs	116	91	78 (S)
Brunschwig	173	141	82 (S)
Christensen	168	137	83 (S)
Masterson	120	105	87.5 (S)

NOT SPECIFIED

Author	Pt. No	Date	Survival %
Currie	189	1971	86.3 (S)
Creasman	266	1986	90 (S)
Artman	110	1987	90 (S)
Morrow	55	1980	92 (S)
Piver	55	1988	92 (S)
Perez	312	1986	85 (RT)
Montan	197	1987	83 (RT)
Piver	48	1988	91.1 (RT)

Lists compiled from *Principles and practice of oncology* (9), and from *Clinical Oncology* (10)

large RTOG study that clearly demonstrates that paraaortic field irradiation added to pelvic irradiation results in a gain of 10% in local control and a decrease of 5% in distant metastases, inter alia for bulky stage IB disease. Combination radiotherapy and surgery are also indicated for adenocarcinomata (8).

RT is a good option where the surgical skills are not optimal. RT may suit the occasional patient better in terms of the logistics a few minutes a day versus 3 weeks or more in capacitation after major surgery. Radiotherapy is also indicated postoperatively where unsuspected infiltrating carcinoma was found following a hysterectomy for some other indication.

EQUIVALENT SURVIVAL WITH SURGERY AND RADIOTHERAPY

Table 1. compares 5-year survival rates obtainable by either modality.

Survival. In terms of survival then, from Table 1, there seems to be little to choose between the two options. According to *Perez et al.* (9) with combined external beam and brachytherapy, the typical 5-year survival rate for stage IB cervical cancer is 86%-92%, and for stage IIA about 75%. The overall pelvic failure rate in stage IB is about 5%-8%, and in stage IIA it is about 15%-20% (in 50 % of the patients combined with distant metastases). Either surgery or adequate radiotherapy is equally effective in stage IB-IIA carcinoma of the cervix; numerous uncontrolled studies support the merits of either modality with no significant difference in survival or pelvic control.

COMPARISON OF SURGERY VERSUS RADIOTHERAPY FOR STAGE IB-IIA CARCINOMA OF THE CERVIX

ADVANTAGES

Surgery	Radiotherapy
Shorter treatment?	
Hospital stay 3 weeks	Outpatient 6 weeks Hospital 2 days
5-year survival rate 83,4% (large collected series)	85,5%
Ovaries conserved in women < 35-40 years	Ovaries irradiated in most patients.
Tumour removal	
Psychological advantage	Patients do worry
Pliable vagina	Sometimes stenosed
Co-incidental adnexal masses or other pathology removed. Accurate staging is possible.	

DISADVANTAGES AND COMPLICATIONS

Surgery	Radiotherapy
Acute complications	
Haemorrhage	Diarrhoea
Febrile morbidity 10-20 %	"Cystitis"
Pulmonary embolism 8%	Latent infection may be worsened
Ureteric stricture/fistula 1-2%	
Bladder dysfunction 3%	
Lymphocysts 1-29% (70% of these in poorly differentiated tumours)	
Damage to obturator nerve-rare	
Femoral nerve compression-rare	
Peroneal nerve compression-rare	

Bladder catheter 14 days or more
for atonic bladder.
(Bladder physiology is grossly altered
by dissection of the lateral ligaments)

Paralytic ileus
Sexual dysfunction
from shortened vagina

The patient may still require
radiotherapy!

Late/Permanent complications

Sometimes urinary diversion
Colostomy
Disfunctional nerve/ bladder

Rectosigmoid stenosis

Vaginal stenosis
Vesico-vaginal or
recto-vaginal fistula
Radiation proctitis
Radiation cystitis
Significant local recurrencerate ofabout 10%
A small risk of
secondary malignancies
Avascular necrosis
of femoral head
(now very rare)
Pyometra from
cervix stenosis
Ovarian ablation and
enforced menopause

RADIATION – INDUCED SECOND MALIGNANCIES The ovaries are not removed when a patient is treated with radiotherapy. This exposes the irradiated patient to a slightly increased risk of ovarian (and other) carcinomata. Since ovarian cancer is a common and deadly cancer it is probably better to have the ovaries removed in the majority of patients, except the very young (11). Normally one in 80 women develops ovarian carcinoma with an expected cure rate of only 30 per cent. This risk is somewhat increased in irradiated patients. A re-exploration rate of 7.6% has been reported (12) with ovarian pathology occurring in the future.

There is also a small excess of other cancers from irradiated organs to be expected, but interestingly according to *Day and Boice* (13) radiation can be expected to ***reduce*** the risk of breast cancer by over 60 per cent, probably because of its effects on the ovary. In women under 40 years of age, and in women over 50 years of age, there is still evidence of a reduction in the incidence of breast cancer by 20 per cent. *Werner-Wasik et al.* (14) disagreed with the reduced risk of breast cancer.

AIDS AND SURGERY VERSUS RADIOTHERAPY A fair number of patients with cervical carcinoma will test positive for HIV. There is an understandable reluctance to operate on these patients, not only because of a risk of infection, but also because these patients are immunocompromised and are not good operative risks. Radiotherapy carries less of a risk, but then intracavitary therapy may have to be left out of the equation, and a teletherapy "boost" needs to be used to supplement central dose to the cervix and immediate paracervical tissues.

FUTURE DIRECTIONS To date, surgical operative staging has failed to realise its aim of improving survival, although it does provide valuable information on the biological behaviour of the disease, and can identify spread to, for example the paraaortic nodes (15). Improved treatment methods to manage patients at risk after surgery are urgently needed.

Radiotherapy has made major strides during the last two decades, and this progress is by no means exhausted. These advances are likely to have a further impact on reducing complications and improving the local control and survival rates for radiotherapy patients. Should the paraaortic nodes be irradiated in patients found to have positive nodes at surgical staging? *Huges et al.* (16) showed that surgical staging, using an extraperitoneal approach, reduced the associated morbidity of extended field irradiation significantly. Proton beam irradiation should be able to improve the outcome of extended field irradiation even further (17-18).

ADVANCES IN BRACHYTHERAPY One of the major advances was the introduction of high dose-rate, remotely controlled afterloading devices. *Fu et al.* (19) showed that the results of high dose-rate and low dose-rate brachytherapy are comparable.

The radiobiological disadvantages of hypofractionation coupled to paradoxically, too many anaesthetics, were solved by developing intra-uterine stents, which enabled radiation oncologists to give multiple fractions with only a single anaesthetic or paracervical block, coupled to simplified dosimetry, rectal and bladder protection and great patient comfort (20-22). For low dose-rate therapy, *Marcial et al.* (23) showed that 2 fractions of intracavitary therapy is better than 1.

Maruyama et al. (24) are trying out 256 Californium, which on theoretical grounds will give better results for local control because of the superior killing of anoxic cells by neutrons.

TECHNICAL FACTORS FOR SUCCESSFUL OPTIMAL RADIOTHERAPY The modern trend is towards 3 dimensional, "conformal" radiotherapy. This simply means that the normal tissues can be spared much better than they are at present. Planning should be done by aid of CT or MRI and perhaps ultrasound, aided by a simulator. The dose should be tailored to the stage of the disease, or in the case of stage IB-IIA, to the volume of the disease (25). New planning systems enable three-dimensional plans to be computed with ease, which in turn will compel radiotherapists to implement "conformal radiotherapy" which will result in better normal tissue sparing despite higher tumour doses, with substantially improved cure/local control rates.

The possibility that proton beams may become as common as

linear accelerators exists, as new research is revealing, e.g. ECRIPAC under development in France.

Newer fractionation schemes can be selected on the basis of tumour cell kinetics. Fast growing tumours should probably be treated by CHART (continuous hyperfractionated accelerated radiotherapy) (26). This combines the advantages of the tissue-sparing effect of small doses per fraction, with the superior tumoricidal capabilities of a short overall treatment time, for selected tumours.

Hyperthermia of the cervix is synergistic with radiotherapy and with cisplatinum, and these options need to be explored.

CHEMOTHERAPY Improvements in the cure rate for cervical carcinoma may depend on more successful systemic therapy. Some chemotherapeutic drugs are active in cervical carcinoma, e.g. bleomycin, peplomycin, and platinum compounds. A promising newcomer is gemcytabine. *Piver et al.* (27) and *Smit et al.* (28) showed that hydroxyurea or cisplatinum can increase the survival rate of patients with advanced carcinoma.

An exciting new development is a thiol compound apparently selectively protecting normal tissues against radiation damage ("Ethyol" or amifostine, Schering Plough Pty. Ltd.).

"ETHIOL" Amifstino (WR 3731, S3 (3 aminopropylaminol) othylphoophorethisis acid; Ethyol, US Bioscience. Inc. West Conshohocken, PA) was developed as a radiation protector. The compound reguires activation by dephosphorylation to produce the free thiol, WE-1065. This process is catalysed by capillary alkaline phosphatase. Additionally, the neutral pH of normal tissues, compared with the slight acidic pH of tumours, favours selective activation. The most likely mechanism for radioprotection involves free radical scavenging and hydrogen donation to repair damaged DNA. The hydrogen ion donation by the thiol group is required for both chemoprotection and radioprotection. Observation shows that the maximum protection can only be obtained if amifostine is given before the administration of cytotoxic or radiotherapy. Amifostine side effects are dose dependent. A dose of 200 mg/kg has been found to be relatively nontoxic, although some hypothermia was observed.

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Radiation therapy versus surgery in early stage cervical cancer

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INTRODUCTION *Joe Vincent Meigs* (1) wrote in 1954: "There is not, nor should there be, any attempt to make the surgical treatment rival radium an X-ray treatment. The two methods are partners in the attack on the disease, for unquestionably some patients will be cured by the one method and not by the other". The debate in relation with the advantages and disadvantages of radiotherapy alone compared with surgery alone or combinations of the two started more than 80 years ago and has continued to the present.

Consensus seems to vary according to the stage presenting for treatment. There is complete agreement that in more advanced stages III and IV, radiotherapy is to be preferred. The choice of treatment is related to earlier stages as I and II and depends on many factors as clinical experience of the treatment team in surgical and radiotherapeutic techniques and on the medical facilities available. Radiotherapist have always argued that a direct comparison of the results obtained with surgery or irradiation is extremely difficult because there is a definite selection of patients. Younger patients, with better general condition and smaller tumors, are generally treated surgically, and patients with less favorable factors receive radiation therapy. Also surgeons (2) and radiotherapists (3) have demonstrated that surgical exploration eliminates those patients with more advanced disease. Therefore it is critical that the results of surgical series be reported based on initial clinical staging.

HISTORIC DEVELOPMENT OF RADICAL SURGERY FOR CERVICAL CANCER In relation with the historical background of the modalities of therapy the first accounts of radical abdominal hysterectomy were published by *Clark* (4) in 1895 in the Johns Hopkins Bulletin and *Wertheim* (5) in 1900. After that *Bonney* (6) in 1935 added to the Wertheims procedure the pelvic nodes dissection. During *Wertheims* (5) and *Bonneys* (6) times every case of cervical cancer was approached for possible surgical resection as primary treatment. Exploration was the determinant of resectability and parametrial induration did not deter them. During that time radiotherapy was the treatment of choice mainly because the cures obtained in stages IIB and III and by the same token surgery rarely cured such advanced lesions and led to disastrous results. In the fifties *Joe Meigs* (7) reintroduced radical pelvic surgery with the obligatory pelvic lymphadenectomy and proposed a different approach. He indicated that the ideal case was stage I, young and in good general health patients, but also most stage II cases. In spite that surgical technique for radical surgery of cervical cancer is the so called *Wertheim-Meigs* operation, it should be remembered that it could be accomplished following different variations. It essentially involves an anatomic dissection of the pelvis, but some prefer to do enblock dissection in continuity of uterus, parametria and lymph nodes. Others remove the uterus and parametria before performing the lymphadenectomy and finally others prefer to do the lymphadenectomy first.

HISTORIC DEVELOPMENT OF RADIATION THERAPY IN CERVICAL CANCER Soon after the discovery of roentgen rays in 1895 and radium in 1898, *Margaret Cleaves* of New York City in 1903 used radium for the first time for the treatment of cancer of the uterine cervix. In 1907, *Dominici* introduced filtration of the radiation from radium. *Dr. R. Abbé* (8) in the United States was the first who cured a patient with cancer of the cervix with radium, with complete clinical regression for 8 years. The Radiumhemmet was founded in 1910 and in 1912 *Gosta Forssel* (9) reported the successful treatment of 24 cases of cervical inoperable cancer with radium. In 1914, the radium treatment for cancer of the cervix was defined as the Stockholm method based on the intracavitary radium application. In 1925, external irradiation was introduced as a complement of radium. The Swedish strategy was a high intensity individualized and intermittent (fractionated) radium treatment as described by *Heyman* (10) and *Kottmeier* (11). During the early part of the century it was also developed the Paris technique at the Institute du Radium by *Regaud* and *Lacassagne* (12). It differs from the Stockholm method in being low intensity, prolonged and single application in small amounts of radium. During the 1930s the Manchester method appeared derived from the Paris method based in physical calculations, where

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predetermined doses are delivered to certain points of reference in the pelvis. After 1970 it was introduced rapid high dose remote afterloading techniques with the main purpose of reducing radiation hazard to personnel. External radiation was initially performed with orthovoltage and after replaced by megavoltage that represented an important step forward. Today intracavitary and external radiation are coordinated differently both in the different clinical stages and in different treatment centers.

It is essential that treatment is individualized with respect to the patient and the tumor. Based on these factors the choice of applicators, the fractionation, the radiation dose and the coordination of the external and the intracavitary therapy is made. According to *Kjellgren* (13), the historical development of the radiation treatment of cancer of the cervix is an example of the trial and error method. Also to obtain good results in this field, either the treating doctor must be a gynecologist trained in radiotherapy, as in Sweden, or there must be a close cooperation between the gynecologist and the radiotherapist. Best results are achieved in centers where great number of patients are treated. Centralization permits comprehensive experience and gaining of knowledge. The high cost of the equipment for intracavitary and external radiation is another factor in favor of the need of centralization of this treatment.

Throughout the period extending from the turn of the century to the middle of the sixth decade, as previously described, radiotherapy was undergoing development with refinement of its techniques and technology. Both surgery and radiotherapy were fraught with problems specific to each method. Both produced urinary tract and rectal fistulas. As *Nelson* (14) said, during the evolution of surgery and radiotherapy the methods were clearly competitive and the competition produced improvements in terms of decreased morbidity and mortality and improved results. Today everybody accords that during the past two decades emphasis clearly shifted from competition to close cooperation between surgery and radiotherapy.

COMBINED THERAPY After 1950, combined forms of treatment have been proposed:

- in 1960, *Stallworthy* (15) introduced a full course of intracavitary radiation followed after 6 to 8 weeks by radical treatment for stages I and II
- in 1975, at the M.D. Anderson extrafascial hysterectomy was preceded by intracavitary and external radiation (16)
- in 1968, *Kolstad* (17) treated in Oslo stage IB with intracavitary (Paris modified) followed by *Wertheim-Meigs*.

Another combined form of treatment is the postoperative external pelvis irradiation after radical surgery upon postoperative discovery of lymphatic metastases by histopathology. It has been for years a controversial question not yet definitely resolved.

REPORTS ABOUT RADIATION AND SURGERY RESULTS IN EARLY STAGE CERVICAL CANCER

FIGO ANNUAL REPORT DATA This Annual Report started in 1937, in Stockholm. Editors have been *Heyman*, *Kottmeier* and *Pettersson* until 1994. Nowadays the editor is *Sergio Pecorelli* in the European Institute of Oncology in Milan. *Kolstad* (18) reviewed treatment results in cervix cancer stages I and II reported in volumes 17 to 20, derived from institutions registering more than 100 cases in each of the stages I and II in the period 1969-1981. In *Table 1.* are presented the results reported from 85 institutions where one treatment predominated are shown.

Table 1. 5-year survival by main method of treatment applied 9720 cases of cervical carcinoma stage IB treated in 1969-78

Treatment method	No of institutions	No cases treated	5-year survival No	%
Surgery	51	5498	4430	80.6
Radiotherapy	23	3241	2141	60.2
Combined Tx	11	981	689	70.2
Total	85	9720	7260	74.7

Tx treatment

It is very probable that a definite selection of patients for surgery or combined treatment has taken place such that those patients with poorer prognosis were treated with radiotherapy.

Table 2. 5-year survival by method of treatment applied 24256 cases of cancer of the cervix stage II treated in 1969-78

Treatment method	No of institutions	No of treated	5-year survival No	%
Radiotherapy	57	14117	7976	56.5
Intracavitary rad., surgery and ext.rad.	29	4213	2229	52.9
Surgery alone or radio Tx alone	30	4984	3210	64.4
Surgery or comb Tx or radiotherapy	5	942	479	50.8
Total	121	24256	13894	57.3

Tx treatment

In *Table 2.* treatment methods and 5-year survival in 24256 stage II cases reported from a total of 121 institutions are shown. Radiotherapy alone was preferred in 14117 cases with a 5-year

survival of 56.5%. Combined treatment followed by external radiation was used in 4213 cases, either surgery alone or radiotherapy alone was the treatment of choice in 4984 cases, and an individualized treatment comprising either surgery alone, combined treatment or radiotherapy alone was reported from 5 institutions with a total of 942 cases. The 5-year survival rates shown in the table are not significantly different.

OTHER REPORTED DATA In non controlled studies as the one of *Brunschwig* (19) either surgery or adequate irradiation is equally effective in stages IB and IIA with no significant difference in survival. Prospective randomized studies as the ones of *Newton* (20) and *Roddick et al.* (21) in stages IB and IIA and *Piver et al.* (22) in stage IB concluded the same. *Perez et al.* (23) in another prospective randomized study compared stage IB and IIA treated with radiotherapy alone or with combined treatment got 80% against 82% 5-year survival respectively. Again in another much more numerous study *Perez et al.* (23) demonstrated no difference between stages IB and IIA treated with irradiation alone and combined treatment. The latest randomized prospective data in unicentric series comparing surgery and radiotherapy in stages IB and IIA of cervical cancer are the ones of *Landoni et al.* (24). The 343 randomized patients were stratified by the size of the cervix. Adjuvant radiotherapy was given after surgery in high-risk cases (positive pelvic nodes, doubtfull margins, etc.). They followed the cases for a median of 47 months for survival and morbidity. The conclusion is that there is not a treatment of choice for stage IB and IIA as regard of overall and disease free survival. The combination of radical surgery and radiotherapy bears the worst morbidity, specifically urologic.

In our experience in the Gynecologic Oncology Unit of the First Gynecology Chair of Buenos Aires University the results of surgery and adjuvant radiotherapy in stage IB1 is 85% 5-year overall survival and in stage IB2, 63%. In stage IIB, our latest results in patients treated with surgery and radiotherapy were 53% of overall survival and in patients treated with radiotherapy alone 50% (25).

In relation with tumor size, *Homesley et al.* (26) found that stages IB greater than 4 cm in diameter treated with radiation therapy alone had a 5-year survival rate of 67%, and the stages IB less than 4 cm in diameter 95% survival. *Mendelhall et al.* (27) with irradiation alone or combined with hysterectomy in stages IB and IIA and IIB, 6 cm greater in diameter also noted no significant difference in pelvic tumor control or absolute survival with either treatment modality.

The postoperative radiation therapy following radical hysterectomy has been studied by *Fuller et al.* (28), *Gonzalez et al.* (29), *Bianchi et al.* (30) and *Bloss et al.* (31) among others. Adjuvant irradiation appeared to benefit patients with multiple positive nodes, but the advantage was not as clear for patients with one to three positive nodes. Although data to support the use of postoperative radiation are not compelling, most gynecologic oncologists will recommend it for patients with positive nodes, preferring to err on the side of providing possibly unnecessary therapy, rather than not providing potentially beneficial therapy. When metastatic pelvic lymph nodes are present, treatment consists of 5000 cGy to the whole pelvis. Patients with positive paraaortic or common iliac nodes should receive 5000 cGy to the paraaortic region as well.

It is a reasonable opinion to indicate external radiation therapy to the following groups of patients:
- Barrel shaped tumors
- Necrotic, hypoxic or anoxic tumors

Table 3. Comparison of surgery versus radiation for stage IB and IIA cancer of the cervix

	Surgery	Radiation
Survival	85 %	85%
Serious complications	Urologic fistulae 1-2 %	Intestinal and urologic strictures and fistulae 1,4-5,3 %
Vagina	Initially shortened, but may lenghten with regular intercourse	Fibrosis and possible stenosis, particularly in postmenopausal patients
Ovaries	Can be conserved	Destroyed
Chronic effects	Bladder atony in 3%	Radiation fibrosis of bowel and bladder in 6-8%
Applicability	Best candidates <65 <80 kg and good health	All patients are potential candidates
Mortality	1 %	< 1% from pulmonary embolism during intracavitary therapy

- Tumors with definite signs of lymph-vascular invasion
- More than four nodes residual on the pelvis
- Involvement of nodes above the common iliac bifurcation
- Metastases that penetrate through the capsule of the nodes
- Adenosquamous or clear cell carcinomas

It is controversial if adenocarcinomas are more radioresistant than squamous cell lesions, but it appears that surgery has a definite place in achieving optimal survival rates.

CONCLUSION Individualization of treatment has been a prominent feature in management of cervical cancer in the last three decades. In stages I and II it is possible to list some factors that may influence the choice of treatment. Such factors should include:

- Age and the preservation of ovarian function. Young patients should preferable treated with surgery.
- Tumor size. Small tumors may well be treated with surgery even in older women. A large tumor and/or endocervical lesion should be treated by the combined method.

Again treatment should be taylored to the patient and centralization of radiation and of surgical treatment are fundamental for the search of excellency.

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Exclusive radiotherapy in the management of carcinoma of the uterine cervix

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INTRODUCTION Radiotherapy of the uterine cervix cancer has a long history which started soon after the discovery of Radium by Maria Sklodowska-Curie and Pierre Curie in 1898. In 1920-1936 C. Regaud, J. Pierquin, G. Richard and O. Monod created at Foundation Curie in Paris the rules of a system using Radium in continuous low dose-rate intracavitary irradiation, ("The Classical Paris System"). After 1930 in the Holt Radium Institute at the Christie Hospital in Manchester *R. Paterson* with *H. Parker* and *J. Meredith* developed a didactic system of brachytherapy published in 1934 as "The Manchester System" (1, 2). During the subsequent decades curative value of brachytherapy in cervical cancer has been well established. The majority of patients have been treated with manual loading system such as those originally developed in Paris, Stockholm and Manchester. These methods were essentially based on the use of Radium as the radioactive isotope and utilized two basic dosimetry systems. The first one was based on the use of certain number of miligrams of Radium for a fixed time of application – miligramhours (Paris, Stockholm) and the second – on distribution of Radium allowing delivery of a constant standard radiation dose rate to defined points adjacent to the cervix (Manchester system – point A) irrespectively of the configuration of ovoids and uterine tube used (1, 3-6). Since the sixties Radium has gradually been replaced by artificial radionuclides (Cobalt-60, Caesium-137 and Iridium-192) and direct insertion of radioactive sources – by manually or remotely controlled afterloading equipment. Subsequently, development of computer programmes, CT scans and MRI images as well as modern dosimetry methods allowed for better definition of dose distribution for an individual patient. Modern brachytherapy afterloading systems permitted for more flexibility and accuracy in administration of intracavitary therapy, proper dosimetry and determination of the dose delivered to various structures in order to improve therapeutic results and provide better protection to the critical organs.

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TREATMENT STRATEGY Radiation therapy plays the essential role in the management of cervical cancer both as an exclusive method or in combination with surgery. The careful selection of patients according to the stage and tumour volume is the first and important step in the treatment. Patients with advanced stages (IIB with extension to the lateral parametrium, III and IV) are always managed by radiotherapy alone which is in these categories the treatment of choice.

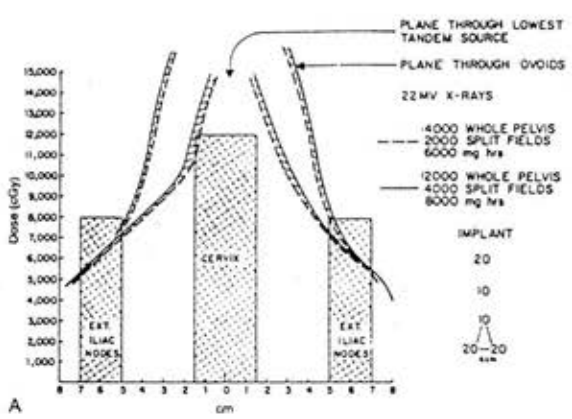
Patients with less advanced stages (IB, IIA and IIB with proximal infiltration of parametrium) can be treated either by combination of surgery and radiotherapy or exclusive radiotherapy. Numerous uncontrolled studies support the merits of either modality but therapeutic decision can sometimes be controversial as many gynaecological surgeons are still in opinion that only surgery is worthwhile considering. However, the results in terms of overall survival and pelvic tumour control obtained with radiotherapy alone or radiotherapy combined with hysterectomy are in stages IB and IIA comparable. The comparison of surgical and radiotherapeutic results pooled from many centres showed 5-year NED survival in 80.8% patient with IB disease treated by hysterectomy and in 77.1% treated by radiation therapy alone (7). *Perez* (8) reported 85% 5-year disease free survival rate in stage IB patients treated with either exclusive radiotherapy or combination of radiotherapy and surgery and in stage IIA the results with these same methods were 71% and 82%, respectively. *Gerbaulet et al.* (9) in a series of 441 cases of IB, IIA and proximal IIB treated by radiotherapy and surgery observed 85% disease free 5-year survival and 5% locoregional failure rate. *Kielbinska et al.* (10) in a long term follow-up of 792 patients given irradiation alone and 789 patients treated with hysterectomy and irradiation for stage I cervical cancer found no difference in survival and in incidence of recurrent carcinoma.

The results of particular studies can vary and cannot be compared directly even if analyzed stage by stage as the tumour size and volume are independent prognostic factors which can substantially influence the results of any therapy (8, 11-12). Nevertheless, it can be generally stated that surgery and radiotherapy are equally effective in the treatment of early stage cervical cancer.

EXCLUSIVE RADIATION TREATMENT The concept of the exclusive radiotherapy of the uterine cervix cancer includes external beam irradiation and brachytherapy. Although the general policy of the treatment is well known, practically, in many various centres treatment is individualised depending on stage, tumour size and configuration, geometry of the pelvic organs, age and performance status of the patients. In most patients exclusive radiotherapy consists of combination of external-beam irradiation of the pelvis followed by 2 intracavitary radioactive sources insertions but in some cases the reverse sequence of the therapeutic modalities is applied (3, 8, 13-15). The total dose distribution in the pelvis depends on contribution of the dose from external beam radiotherapy and brachytherapy which will differ in particular cases according to the tumour volume and stage of the disease.

According to the *ICRU Report No. 38* (5), "An absorbed dose level of 60 Gy is widely accepted as the appropriate reference level for classical low dose rate brachytherapy. When intracavitary therapy is combined with external beam therapy the isodose level to be considered is the difference between 60 Gy and the dose delivered at the same location by external beam therapy". However, in dose specification, there is considerable complexity since both central volume containing the tumour and peripheral volumes encompassing the regional lymph nodes are irradiated partially by intracavitary and partially by external beam techniques. The contributions thereof and the corresponding dose rates may vary considerably, leading to large variations in biological effects. Consideration of brachytherapy dose gradient at lateral parts of the pelvis and external beam dose to the pelvic lymph nodes resulted in modifications of external beam technique, especially in use of central shielding which can vary from a slab midline block to a carefully designed 3D individualized step wedge (4, 8).

Although doses are normally combined straightforwardly as brachytherapy Grays plus external beam Grays, in fact, due to dose rate variables between brachytherapy and external beam therapy, the effective biological dose may differ considerably (4, 16). It should therefore be stressed that exclusive radiotherapy of the cervical cancer requires properly planned and performed treatment with well controlled dosimetric parameters for tumour and normal tissue (*Figure 1*, from *Perez (8)*).



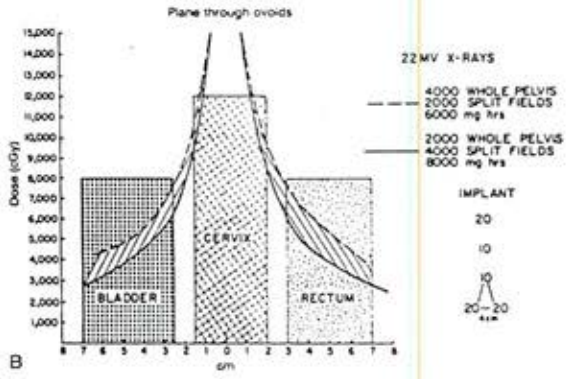


Figure 1. Dose profiles in the coronal (A) and sagittal (B) planes for patient with carcinoma of the uterine cervix treated with 2000 cGy to the whole pelvis and 8000 mgh or 4000 cGy to the whole pelvis and 6000 mgh. Additional dose to the parametria is delivered to complete 6000 cGy. The dose distributions are comparable in the coronal plane. However, on the lateral projection the technique using 2000 cGy to the whole pelvis and 8000 mgh (7200 cGy to point A) delivers about 2000 cGy less to the bladder and rectum. This should result in better tolerance for comparable tumor doses.

EXTERNAL BEAM RADIATION TREATMENT

Target volume 1. Whole uterus, 2. Whole pelvis, 3. Upper two thirds of the vagina, 4. Pelvic and common iliac lymph nodes

Energy High-energy photons 10-25 MeV of linear accelerator or Cobalt-60 unit

Techniques 2 parallel opposed fields 15 x 15 cm up to 15 x 18 cm or 4 field "box" technique

Doses and fractionation *Central pelvis:* 20 to 45 Gy (according to stage) 5 x 2 Gy weekly. *Lateral pelvis:* 40 to 55 Gy (according to stage) 5 x 1.8 Gy weekly. *Boost to the infiltrated parametrium:* 10 Gy - 5 x 2 Gy weekly in selected cases according to the stage and individual treatment policy.

BRACHYTHERAPY TECHNIQUES The endocavitary brachytherapy is an essential part of the treatment of cervical carcinoma due to the following advantages:

- delivery of a significant dose during a limited period of time to a relatively small volume of tissue;
- sparing the surrounding normal tissue because of rapid dose fall-off around the sources as a function of distance;
- dose rate allowing tissue repair (4, 17).

Nowadays, with wide use of brachytherapy in the management of cervical cancer, there is a large number of available technological, physical and biological options. In order to make an optimal approach on the rational basis, the following aspects are to be taken under consideration:

Applicators Intracavitary treatment requires an intrauterine tube and vaginal applicators containing radioactive sources. The importance of selecting the appropriate applicators has been stressed by *Fletcher* (18) in his classical paper. Many

kinds of applicators have been designed and succesfully used in brachytherapy departments. Among them the most widely used are: *Fletcher-Suit-Delclos* applicators with sources perpendicular to the axis of vagina, *Delouche* colpostats with Caesium sources parallel to the axis of vagina, individual vaginal moulds, *Henschke* applicators and others suitable for particular afterloading machines (8, 13, 15, 17).

Radioactive sources Formerly used Radium has been succesfully replaced by Caesium-137, Cobalt-60 and Iridium-192. There is no ideal source and their use is dependent on the technique used (LDR, MDR or HDR).

Afterloading techniques There are many remote afterloading machines for brachytherapy available at the market allowing for selection to suit the best all the departmental requirements.

Dose-rate Three comparatively well defined dose-rate catagories are utilized in cervical cancer brachytherapy (4): 1. LDR – 0.4-2.0 Gy/hr, 2. MDR – 2.0-12.0 Gy/hr, 3. HDR – Any dose rate graeter than 12 Gy/hr (0.2 Gy/min) but usually 2.5 Gy/min.

Total dose and fractionation The recommended dose defined in *ICRU Report No. 38* (5) as reference isodose is 60 Gy. Usually in LDR brachytherapy this dose is given in 2 fractions. Sometimes 3 fractions are used according to the stage and contribution of external beam irradiation (3-4, 8, 13).

Calculations and dosimetry According to the *ICRU Report No. 38* (5) the volume of tissue to be irradiated is a pear-shaped, flattened anteroposteriorly. Therefore, the required dose distribution is trefoil in shape, providing maximal dosage towards the parametria laterally as well as to the uterus and vagina but with minimal irradiation towards the bladder and the rectum. Computed dosimetric calculatios made in 3 planes can programme the appropriate loading irrespectively of the lenght of intrauterine tube and size of vaginal ovoids:

- either to produce the pear-shape reference isodose of 60 Gy adjusted to required height, width and thickness of the tumour volume,
- or to deliver a standard radiation dose (or dose-rate) to the reference points at target volume: both points A, both points B, pelvic wall, pelvic lymph nodes with calculated possibly lowest dose to the different critical organs: bladder, rectum, small bowel etc.

In planning of the treatment two facts are therefore of particular importance:

- volume of the tissue to be given therapeutic dose
- tolerance of the relevant tissue.

It has to be stressed that size of the pear-shaped isodose is different in particular cases because of the individual anatomy, tumour size, tumour shape and stage of disease as well as the changes in the local anatomy during radiotherapy resulting from shrinkage of the tumour and decreased size of vagina and uterus (3, 13, 15, 19). Accurate source positioning in relation to the tumour mass and the normal anatomical structures must be checked up by PA and lateral pelvic radiography. Additionally *in vivo* dosimetry is recommended (3, 8, 13, 17).

RESULTS In order to evaluate the results obtained by exclusive radiotherapy in aspect of local control, survival and complication rate, various prognostic factors are to be taken into consideration: 1. stage, 2. tumour volume, size and configuration, 3. geometry of the pelvic organs, 4. age and performance status of the patients, 5. dose delivered, 6. dose-rate, 7. treatment time

The *Stockholm Report* of 1988 (20) on the results of treatment in gynaecological cancer presented the amazing number of 476 747 cases of carcinoma of the cervix treated between its first report in 1913 and the latest of 1981. In that report there was still a large variation in 5-year survival rates reported by stage by 73 different institutions. 5-year survival varied in stage I from 55% to 97%, in stage II between - 40% and 87% and in stage III - between 5% and 60%, although for each stage a modal figure may by calculated: stage I - about 85%, stage II - about 60% and stage III - about 25%. *Perez et al.* (8) presented in 1983 results of 849 patients treated with exclusive radiotherapy, which showed 5-year survival rates in stage IB - 87%, IIA - 73%, IIB - 68%, III - 44% and IV - 0%, with pelvic recurrence rates of 6.4% in stage IB, 12.5% in stage IIA, 17.4% in stage IIB, 35.8% in stage III and 75% in stage IV. *Horriot et al.* (21) in the report on results of exclusive radiotherapy in cervical cancer obtained in a French cooperative study of 1383 cases presented one of the best results in the literature. Five-year disease free survival has been observed in 76% of patients in stage IIB, 62% patients in stage IIIA and in 50% in stage IIIB with significant dependence of locoregional failure rate on stage: 7% of recurrences in stage I and IIA and 16% - in stage IIB.

Since the results of overall survival and locoregional control have remained unchanged for years, the efforts have been focused on finding some other prognostic factors which influence the results of treatment. One of the most important prognostic factors seems to be the size and shape of the tumour. It is believed that bulky disease with barrel shape cervix and tumour greater than or equal to 6 cm carries high incidence of local recurrence, lymph node metastases and distant dissemination (8, 11-12, 22). *Lowrey et al.* (12) revealed in a multivariate analysis of 306 patients of stage IB, IIA and IIB that only tumour size was an independent prognostic factor for pelvic control, distant spread and relapse-free survival. Also *Horriot et al.* (22) in a series of 1530 patients with carcinoma of the cervix treated with radiotherapy alone from 1970 to 1983 found significant relationship between tumour volume and risk of loco-regional failure and dissemination.

There is also evidence of influence of the total dose and overall treatment time on the results of exclusive radiotherapy in cervical cancer. *Choy et al.* (23) analysed the impact of the point A dose in a range of 40 to 100.9 Gy on the results in 594 stage IB-IIIB patients with cervical cancer. Dose - local control relationship was demonstrated for stages IIB - III with better

local control associated with higher dose (up to 85 Gy) to point A. An analysis of the cervical and vaginal recurrence as a function of avarage total dose to paracentral points done by *Montana et al.* (6) showed a recurrence rate of 34% with a dose less than 65 Gy but only 14% with a dose of 75-80 Gy. No correlation was observed above a dose of 80 Gy. In the retrospective analysis of 1211 patients with cervical cancer treated by exclusive radiotherapy *Perez* (8, 14, 24) found that the point A dose below 60 Gy resulted in 66.7% and 72% of pelvic failure rate for stages IIB and III, respectively but with increase a dose to 60-90 Gy the pelvic failure rate decreased to 23.4% and 39%, respectively. The dose higher than 90 Gy had a very little impact on results. No significant correlation between doses to point A and pelvic recurrences was seen in stages IB and IIA. *Perez et al.* (8) also found that if the dose delivered to lateral parametrium was less than 40 Gy the recurrences was encountered in 71% of cases. In contrary, for the doses of 60-65 Gy pelvic failure rate was 39-40%. The similar relationship was found between the dose to medial parametrium and recurrence rate independently of the stage.
(*Figure 2*, from *Perez* (8)).

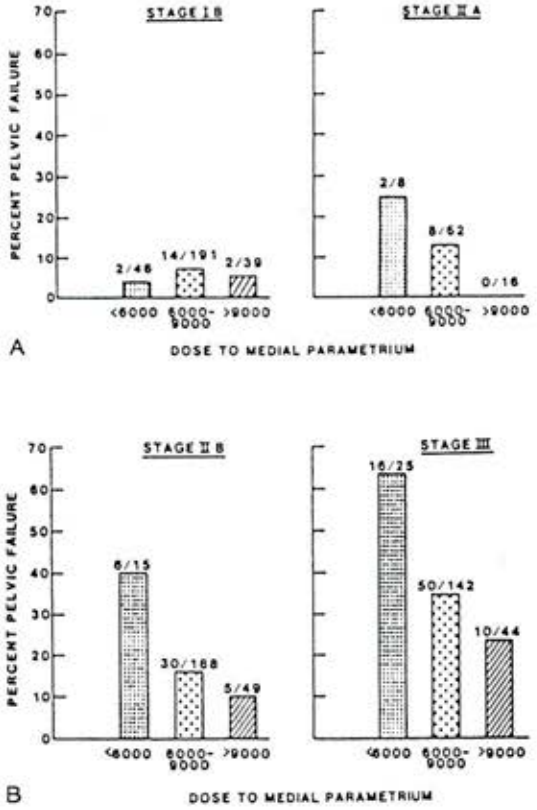


Figure 2. (A and B) Local/marginal parametrial recurrences correlated with dose to medial parametrium (0.8) in patients with stage IB, IIA, IIB, or III carcinoma of the uterine cervix. Decreasing parametrial recurrences are noted with higher doses of irradiation in stage IIA and greater. (Perez CA, et al. Cancer 1983; 51:1393)

Another important issue is the impact of prolongation of overall treatment time and timing of brachytherapy on survival and local recurrence. *Perez et al.* (25) demonstrated a strong correlation between overall treatment time and pelvic recurrence rate. After the analysis of 1224 cases he found that prolongation of overall treatment time resulted in decreased pelvic tumour control rate of 0.85% per day for all stages regardless of tumour size, except for tumours less or equal to 3 cm in stage IB. *Petereit et al.* (26) showed that prolongation of total treatment time over 55 days resulted in decreased survival (0.6% per day) and decreased pelvic control (0.7% per day) for all stages. Also *Girinsky et al.* (27) found the overall treatment time to be a highly significant prognostic factor in the treatment of advanced cervical cancer; loss of local control and overall survival was in his series approximately 1% per day if overall treatment time exceeded 52 days. These results suggest that prolongation of treatment time in patients with cervical cancer is associated with decreased local control and overall survival.

COMPLICATIONS The major complication rate after exclusive radiotherapy ranges from 3 to 5% for stages I and IIA carcinoma of the cervix and from 10 to 15% for stages IIB and III (8). The most frequent sequelae include rectal, recto-sigmoid and bladder reactions.
Horriot et al. (21) in the analysis of 1530 patients with cancer of the uterine cervix treated by radiotherapy alone using the French-Italian glossary for identification of early and late tissue damage found that 40% of cases developed some complications, out of them 46% was of grade G_1, 39% – G_2, 13% – G_3 and 1.8% – G_4, leading to death. In his series bladder complications were observed in 20%, rectal – in 17%, sigmoid – in 7% and small bowel in – 3% of patients.

There is a correlation of incidence of grade 2 and 3 complications with the dose of radiation delivered to the organs (8, 13-14). In 1984 *Perez et al.* (14) found grade 2 and 3 bladder and rectum complications in about 5% of cases if the delivered dose to those organs was up to 80 Gy and in 15% of those with the dose above 80 Gy. The actuarial incidence of major rectal and recto-sigmoid complications presented by *Perez et al.* (24) in 1991 was also dose dependent. With the dose to the rectum of 60-80 Gy complications were observed in 2-4% of cases, with 80-95 Gy – in 7-8% and in those with the dose higher than 95 Gy – in 13%. *Haie-Meder et al.* (28) performed a prospective randomized trial to define relationship between the dose rate and results and complications in exclusive radiotherapy of cervical cancer. At 2 year follow-up time the total incidence of all complications, regardless of their nature and severity, was observed in 75% of cases treated with the dose rate of 0.8 Gy/h and in 63% of those treated with the dose rate of 0.4 Gy/h, whereas severe complication rates were 13% and 7%, respectively.
Prevention of complications should be based upon treatment individualization. The treatment planning based on general guidelines should be modified in particular patient depending on the initial extent of disease, tumour volume and shape, individual anatomy and rate of regression during external beam irradiation. The careful brachytherapy should be individually adjusted to provide the appropriate dose distribution in the pelvis with the total dose therapeutic to the tumour and minimized dose to the critical organs.

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The management of advanced and recurrent carcinoma of the cervix

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INTRODUCTION It is an unfortunate fact that stage IIB, III and IV carcinoma of the cervix is still frequently seen, especially in patients of lower socio-economic status. The very people who need PAP smears the most, get it done the least often. There is also a tardiness from the side of Government in many instances to support large-scale screening programs. WHO recommendations suggest the first screening should take place at 35 years of age, but in fact the damage is done to the transitional zone by the papilloma virus and possibly by trauma, long before that age. Many people in the lower socio-economic strata participate in sex shortly after the menarche, so that there is already ten years that the virus had time to transform the cells, and even at the age of 25 then, many females are already saddled with CIN II or III, or even invasive carcinoma. Education and screening, should in the opinion of the members of our Combined Clinic in Tygerberg, be started at an early age, certainly no later than age 25.

THE MANAGEMENT OF ADVANCED CARCINOMA OF THE CERVIX The best management would be prevention. However, when faced with an advanced carcinoma, the treatment is mainly radiotherapeutic.

STAGING Proper staging in a combined clinic is very important, and an adequate work-up is essential to exclude metastatic disease. This includes a bone scan, cystoscopy, chest x-ray, sonar of the liver, intravenous pyelogram to exclude hydronephrosis, and blood tests to test the haemoglobin levels and other relevant parameters, as well as kidney and liver functions. Patients with hydronephrosis seldom fare well, but if the patients are of good performance status, with adequate haemoglobin levels, it is our policy to treat and if all goes well, to persist to a radical dose.

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PLANNING AND SIMULATION Planning should be done *by means of a CT* scan wherever possible, as it is important to encompass all detectable disease properly. The fault that is commonly made by simple simulation, is that the extent of the disease posteriorly and lateral to the rectum is underestimated. Similarly, disease can often be seen on CT planning to extend anteriorly and make a bulge into the bladder, even if the bladder is not infiltrated. The superior limit of the disease is difficult to define, and the entire fundus should be included. Sometimes a myoma can be ignored from the treatment volume if the latter is calcified, which may signal a benign confounding factor. It is very important to make exact sketches of the extent of the tumour and to carefully note the extent of extension into the vagina especially to the middle or lower third, in order to ensure proper coverage of the disease. The extent of parametrial involvement must be recorded carefully prior to planning. Unilateral pelvic extension, especially to the right parametrium, may prompt a note on the prescription form to consider additional irradiation to the affected side, especially where the response is not adequate by the time the external beam radiotherapy is completed.

The patient should be re-examined on the CT scanner bed (which should be flat, like the treatment couch). A tampon, of which the tip has been dipped into a radio-opaque dye, should be used to mark the inferior limit of the tumour. The treatment fields should extend well below this marker for 2 reasons: firstly to anticipate microscopic subepithelial creep, and secondly, because three dimensional reconstruction of isodose curves in the sagittal plane, will show a distinct tendency to "contract" about 1 cm in the saggittal plane.

Wherever possible, the patient should be scanned, and treated with a full bladder. This helps to displace the more sensitive intestine out of the high dose zone.

The upper limit of the field is perhaps of lesser importance than the cervical and parametrial zone; local control is the primary objective. Field lengths are typically about 14 to 16 cm, but where disease comes down low in the vagina, the fields may reach 18 cm or more in length, and to treat such long fields to a high dose is probably to invite serious compli-

cations. Faced with such a situation, the trend should perhaps be to rather cut a centimetre or two off the superior border. The patient should be treated with multiple fields, all treated every day rather than with two parallel opposing fields. We commonly use a fourfield "box" technique. Field shaping is difficult where a large patient load faces a department, but should be attempted or the possibility assessed for each patient.

BEAM ENERGY The best dose distributions are obtained with 8-16 MeV photons, depending on the separation (thickness) of the patient. Lower energies should probably be avoided.

FRACTIONATION The fraction size should be 1,8 Gy to 2 Gy per fraction, and no larger. The routine at Tygerberg is to use 27 fractions to the whole pelvis to a total dose of 54 Gy in 33 days, supplemented by four doses of 4 Gy to "point A" intracavitary treatment daily, total 16 Gy, to a total dose of 70 Gy at "point A", giving a total treatment time of 38 days. The intracavitary treatment is by means of an ^{192}Iridium remotely controlled afterloader, the "Gammamed II" from Isotopen Technik Sauerwein.

INTRACAVITARY THERAPY It has been shown by *Hanks et al.* (1) that the intracavitary therapy is crucial to the optimal therapy for late stage disease – especially to control central recurrences. The technique used in our institution is that described by *Smit et al.* (2-4). This technique briefly, comprises the insertion of an indwelling nylon tube or stent into the uterus on day 33. This tube is inserted under local anaesthesia (a paracervical block with about 10-15 ml of 1% lignocain injected paracervically), or by a brief general anaesthetic. The tube is left in position for advanced carcinoma for 5 days. With practice, four patients can be fitted with tubes per hour. This tube makes it extremely easy to relocate and accurately place the usual intracavitary applicators daily for 4 days with great comfort to the patient. (Four fractions of 4 Gy each delivered to "Point A"). A Foley's catheter is cut at the side, the applicator threaded through so that the bulb surrounds the applicator. This gives an unobstructed view of the tube in the uterus, and the bladder and rectum are then displaced away from the high dose zone by water injected into the bulb of a 40 ml Foley's catheter.

This system allows adequate and flexible irradiation of the fornices, and in fact gives superior irradiation to the parametria compared to the more conventional colpostats, which irradiate the paracolpos mainly, and also delivers an unnecessarily large dose to the vaginal surface, despite the risk of a cold spot on the cervix! For the same AP diameter of the isodose as obtained with colpostats, the sparing of the bladder and rectum are not inferior. With this system, the patient is irradiated with a full (but not overdistended) bladder, which ensures autoprotection of the anterior and lateral walls of the bladder. Superior fractionation, with better radiobiological sparing of the normal, late reacting tissues, is achieved without supernumerary anaesthetics. Careful dosimetry with CT scans with the applicator system *in situ* showed that the bladder and rectal doses are within acceptable, and reproducible limits *(Figure 1a and 1b)*.

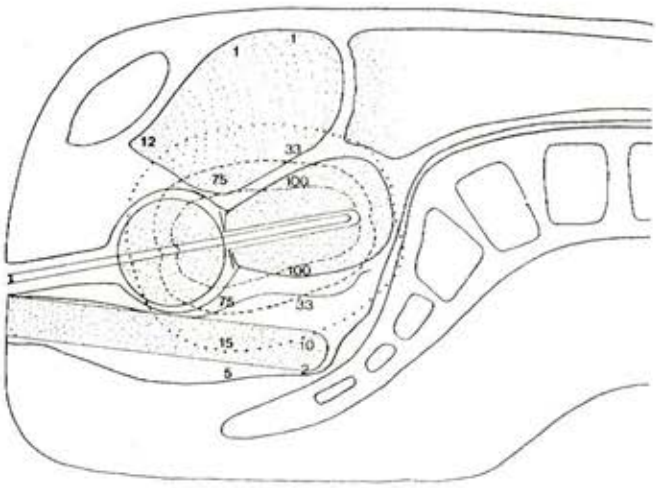

Figure 1. Dosimetry of the indwelling uterine tube/Foley bulb system, determined with diodes in position. Doses at sites not accesible by diodes, calculated by using the inverse square law. The correlation of measured and calculated doses were good.

TOTAL TREATMENT TIME The time of the treatment is important. The longer the overall treatment time, the worse the prognosis with a highly significant difference between overall treatment times of <6, 6-7.9, 8-9.9 and 10+ weeks (5). Our own overall treatment time is 38 days i.e. <6 weeks. The total treatment time with the above scheme is 38 days, the total TDF 90 (external) plus 40 (intracavitary to point A) so that the total TDF to point A is 130 (6). *Chougule et al.* (7) showed that for carcinoma of the cervix the TDF and TSD concepts predicted probable tumour response as well as the LQ model. A narrow, 3cm wide "boost" is sometimes give to persistent involvement of, especially the right parametrium (less risk than the left parametrium with the rectosigmoid in the field) The field length for this boost is usually no longer than 8-10 cm, and is given with 8-16 MeV photons by two parallel opposing fields.

With this approach, an actuarial survival rate for stage III carcinoma of 60 per cent, and an absolute 5 year survival of 39,7 per cent was achieved in 732 patients (8). The complication rate was low, 6% for late grade 2-3 cystitis/proctitis.

CHEMOTHERAPY AS SENSITIZERS Various efforts have been made to improve the 5 year survival of patients with advanced carcinoma of the cervix. The better "complete response rates" achieved with combination chemotherapy appears to be 29 per cent, with a combination of mitomycin-C, vincristine, bleomycin and cisplatinum (in 14 patients), and with doxorubicin and methyl CCNU (31 patients) (9). *Smit et al.* (10) showed an actuarial survival of 60% (RT alone); 84% (RT+ Cisplatin) and 85% (RT+ Hydrea) in a small controlled study *(Figure 1.)* confirming findings by *Piver et al.* (11). Further references on this topic are obtainable in *Perez* (9). Complications were not

Table 1. Complications of combined radiation and chemotherapy (10)

EARLY COMPLICATIONS

Treatment arm	Cystitis No (%)	Proctitis No (%)	Diarrhoea No (%)	RVF/ VVF
RT alone (20 patients)	3 (15)	1 (5)	1 (5)	–
RT+Cisplatin (21 patients)	1 (4.7)	–	3 (14.2)	–
RT+Hydrea (22 patients)	2 (9.1)	1 (4.5)	3 (13.6)	–

LATE COMPLICATIONS

Treatment arm	Cystitis No (%)	Proctitis No (%)	Diarrhoea No (%)	RVF/ VVF
RT alone (20 patients)	–	2 (10)	–	–
RT+Cisplatin (21 patients)	2 (9.5)	1 (4.7)	1 (4.7)	–
RT+Hydrea (22 patients)	1 (4.5)	2 (9.1)	2 (9.1)	–

RVF Recto-vaginal fistula VVF Vesico-vaginal fistula

severe *(Table 1.)*. Recently, gemcytabine has been identified as an active drug (12).

MANAGEMENT OF RECURRENT CARCINOMA This is always a very frustrating, usually debilitating, but not always fatal occurrence. *Monaghan* (13) is very positive in his approach to recurrent disease. According to this source, survivals with exenteration now reaches 40% to 60% in recently reported large series. This reader is referred to this excellent review of this subject.

An absolute contraindication is distant metastases. Relative contraindications to surgery include spread to the pelvic sidewall, the triad of unilateral leg oedema, sciatic leg pain and unilateral uropathy is an ominous sign. Obesity and a poor mental orientation by the patient are risk factors.

Survival at 5 years varied from 18 per cent to 61,8 per cent, so that it is obvious that this procedure may offer some hope to a substantial number of otherwise hopeless patients, but the price in morbidity is relatively high.

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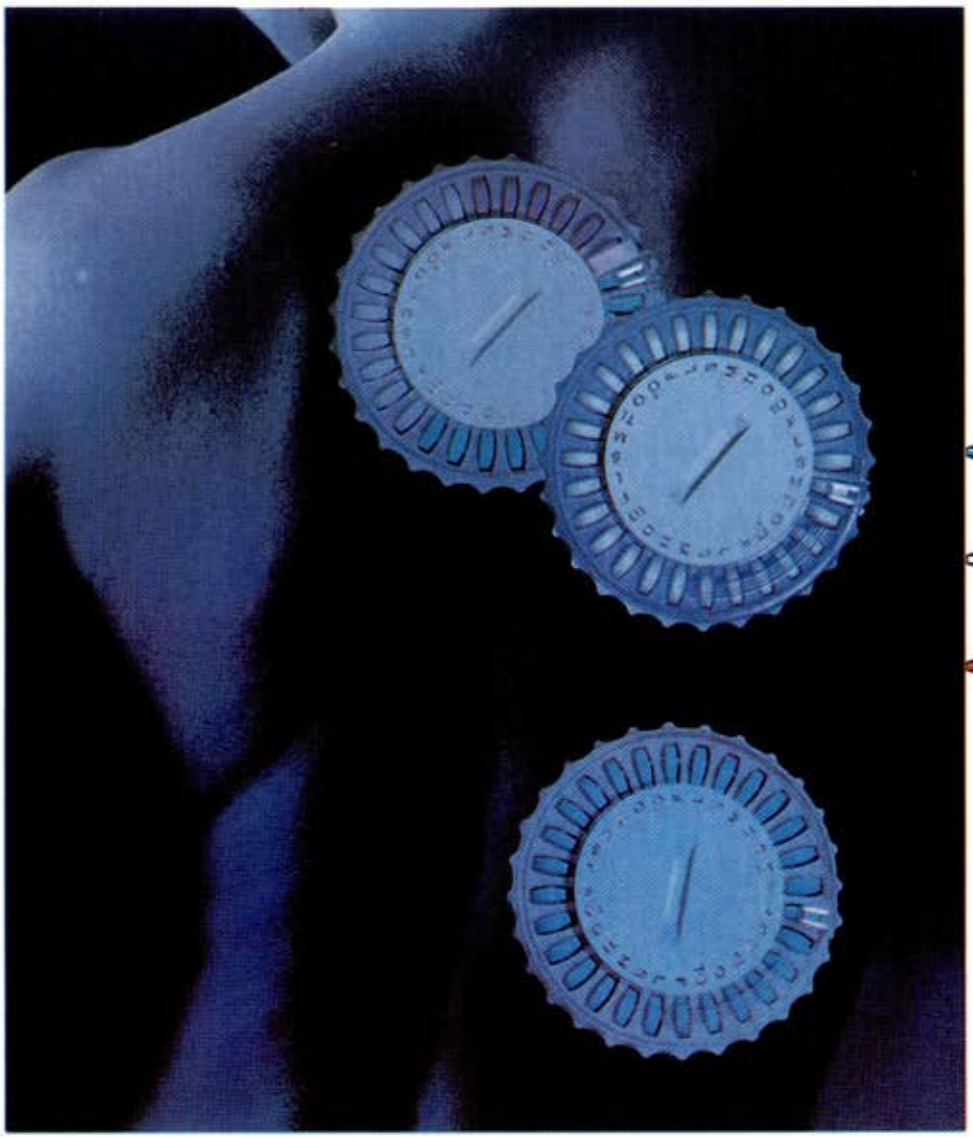

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Figyelmeztetés: A kezelés csak a tumorellenes kemoterápiában jártas orvos által vagy felügyelete mellett végezhető. A tartós kezelés esetén csak rendszeres szakorvosi kontroll mellett alkalmazható. Minden egyes rendellenes menstruációs vagy hüvelyi vérzés és/vagy váladékozás, továbbá alhasi fájdalom azonnali szakirányú kivizsgálást, illetve kezelést igényel.

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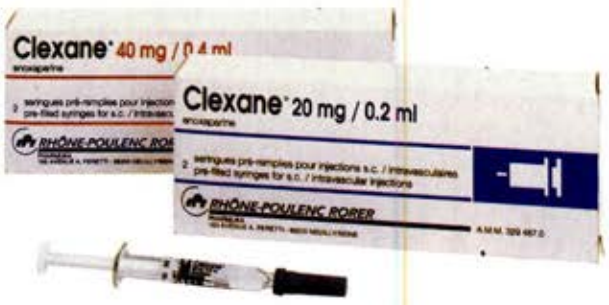

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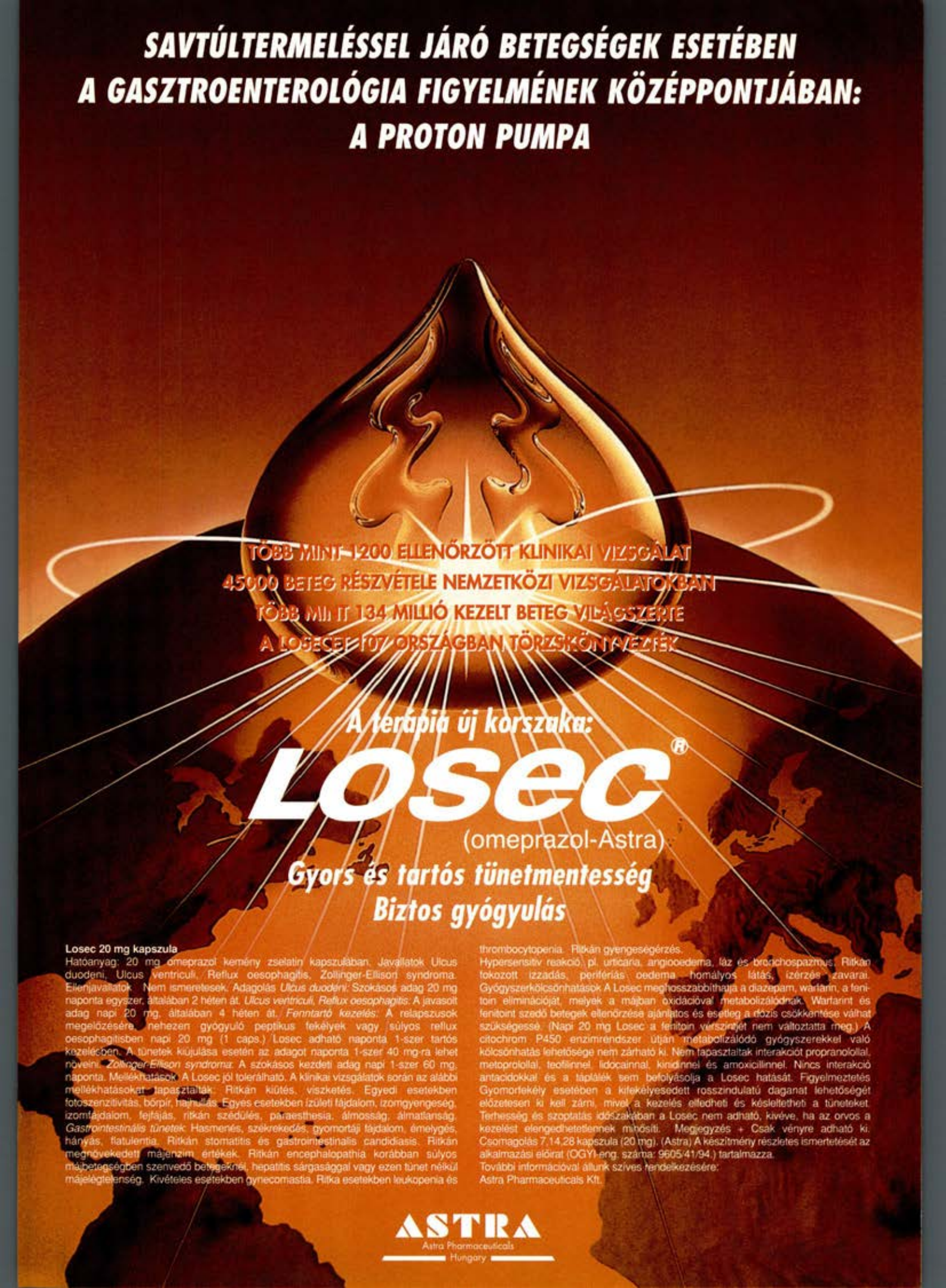

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Hypersensitiv reakció, pl. urticaria, angiooedema, láz és bronchospazmus. Ritkán fokozott izzadás, perifériás oedema, homályos látás, ízérzés zavarai. Gyógyszerkölcsönhatások A Losec meghosszabbíthatja a diazepam, warfarin, a fenitoin eliminációját, melyek a májban oxidációval metabolizálódnak. Warfarint és fenitoint szedő betegek ellenőrzése ajánlatos és esetleg a dózis csökkentése válhat szükségessé. (Napi 20 mg Losec a fenitoin vérszintjét nem változtatta meg.) A citochrom P450 enzimrendszer útján metabolizálódó gyógyszerekkel való kölcsönhatás lehetősége nem zárható ki. Nem tapasztaltak interakciót propranolollal, metoprololl, teofillinnel, lidocainnal, kinidinnel és amoxicillinnel. Nincs interakció antacidokkal és a táplálék sem befolyásolja a Losec hatását. Figyelmeztetés Gyomorfekély esetében a kifekélyesedett rosszindulatú daganat lehetőségét előzetesen ki kell zárni, mivel a kezelés elfedheti és késleltetheti a tüneteket. Terhesség és szoptatás időszakában a Losec nem adható, kivéve, ha az orvos a kezelést elengedhetetlennek minősíti. Megjegyzés + Csak vényre adható ki. Csomagolás 7,14,28 kapszula (20 mg). (Astra) A készítmény részletes ismertetését az alkalmazási előirat (OGYI-eng. száma: 9605/41/94.) tartalmazza.

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Radiation therapy of recurrent cervical carcinoma

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ABSTRACT Despite the relatively high success rate of treatment for early stage cervical cancer there remain a significant number of patients who recur locally and eventually die because of inadequate local control. Salvage therapy for patients treated with radical hysterectomy may be irradiation with good local control rates especially for central recurrences. Patients who fail after radiotherapy or combined surgery and irradiation represent a therapeutic challenge: patients with central relapses may be salvaged by pelvic exenteration; side-wall recurrences are best managed by aggressive treatment approaches such as CORT.

Key words: recurrent gynecologic cancer, cervical cancer, radiotherapy

INTRODUCTION Despite the relatively high success rates of both surgery and radiotherapy in the treatment of cancer of the uterine cervix, there remain a significant number of patients who fail locally after standard therapy. Pelvic recurrences from carcinoma of the cervix typically occur within 24 months of treatment and show relatively similar distributions independently of the initial treatment approach: 5-15% in FIGO stages IB-IIA, 20-45% in stages IIB-III (1). Even in stage I cervical cancer, in spite of effective treatment methods with radical hysterectomy or irradiation, up to 15% of patients suffer from local recurrences and eventually die because of inadequate local control (2). There is general agreement on the fact that a single modality of therapy is preferable to combining major therapeutic interventions, so that the second modality can be used as a form of salvage therapy. Positive or close surgical margins following radical hysterectomy as well as the finding of lymph node involvement, however, do mandate postoperative irradiation. There is no general consensus as to the indications for adjuvant irradiation in patients with other risk factors that contribute to higher local recurrence rates (3).

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The most important risk factors for local recurrence in carcinoma of the cervix can be summarized as follows:

Lymph node involvement pelvic lymph node involvement is the strongest predictor of pelvic failure in early cervical cancer. Moreover pelvic lymph node involvement is predictive of an unfavorable prognosis after radical hysterectomy and pelvic lymphadenectomy: the 5-year survival rate of about 90% for patients with stage IB disease with negative lymph nodes drops to about 55% when one or more lymph nodes are involved (1, 4). Patients with one to four positive lymph nodes have a 48% 5-year survival rate compared to 19% for women with more than four involved nodes. Bilateral nodal involvement above the iliac artery bifurcation has a less favorable prognosis than unilateral lymphatic involvement or disease below the bifurcation (2).

Tumor size the importance of cervical lesion size on pelvic lymph node spread was shown by *van Naggel et al.* (5) in a series of patients treated with radical hysterectomy and lymphadenectomy. Cervical lesions less than 2 cm in diameter showed nodal disease in 9% of patients compared to 31% of those with larger lesions. The difference in terms of local tumor recurrence rates were even more striking with 9% of patients with lesion smaller than 2 cm developing recurrence versus 44% of those with larger lesions. Bulky stage IIA lesions (barrel-shaped tumors) with diameters 6 cm and above have significantly higher local recurrence rates (6, 7).

Stromal penetration increased depth of stromal penetration correlates with higher pelvic recurrence rates and decreased survival (8).

Vascular invasion the presence of tumor cells in arterial, venous and lymphatic vessels correlates with a poor outcome in cervical cancer. *Boyce et al.* (9) showed a 5-year recurrence-free survival of 86% in patients with no vascular involvement and a cervical invasion of 5 mm or more versus 60% recurrence-free survival in patients with similar stromal penetration but with vascular involvement.

Extension to the corpus Perez et al. (10) reported a 10-15% lower survival rate in patients showing endometrial extension for all stages. According to *Boyce et al.* (8) patients with endometrial extension have a 4.8-fold increased risk of developing recurrent disease compared to those without corpus invasion.

When pelvic lymph nodes are negative for tumor involvement, the presence of one of these additional risk factors does not

worsen prognosis in terms of local recurrence to such an extent as to justify different treatment strategies. The assessment of these risk factors at initial evaluation of the patient may indeed contribute to an appropriate selection of those patients who appear to have a more aggressive disease and whose treatment may therefore consist of a combined chemo-radiation approach rather than radical surgery, so as to reduce the likelihood of local relapse (3).

When the pelvic relapse arises the treatment options for salvage are considerably dependent on the site and extension of the lesion, as well as previous treatments received by the patient. In general, three different pelvic recurrence sites are recognized: central recurrences, pelvic side-wall recurrences and bilateral side-wall involvement (11). The clinical presentation of recurrent cervical cancer is variable and depends on the site and extension of the relapse: usual symptoms of central recurrences are vaginal discharge and bleeding, whereas pelvic side-wall recurrences may cause pain and swelling of the lower extremities. It is important to make an early diagnosis of recurrent disease, as prognosis largely depends on the extent of the recurrence, and since the great majority of recurrences arise within the first two years after initial treatment, follow-up visits should be relatively frequent during this time interval. The treatment options for recurrent cervical cancer largely depend on the previous therapeutic approach. This article will focus on the treatment of recurrences after previous surgery alone, after radiotherapy alone or combined surgery-radiotherapy; it will also address the issue of combined chemo-radiotherapy and of more innovative approaches such as intraoperative radiation therapy (IORT) and combined operative and radiotherapeutic treatment (CORT).

RECURRENCES AFTER SURGERY Pelvic recurrences in patients who have been treated surgically and have never received irradiation can be managed successfully with radiation therapy. The results of radiation therapy differ considerably according to the site and extent of the pelvic relapse as well as of the aggressiveness of the treatment, with doses below 60 Gy yielding local control rates of only about 5% (12). The long-term survival rate for central recurrences is better (30-80%) than for pelvic side-wall recurrences (5-30%), (13). *Friedman and Pearlman* (14) reported a 42% disease-free survival in 38 patients treated with irradiation after primary surgical therapy. Of 14 patients with limited central recurrences, 8 (57%) were disease-free from 3.5-9 years. Patients with side-wall recurrences had the worst results (only 3 of 11 patients survived tumor-free more than 5 years). *Larson et al.* (15) reported on 249 patients treated with radical hysterectomy and lymphadenectomy for stage IB: they observed 27 relapses (11%) 15 of which were treated with radical radiotherapy; 8 (63%) of these patients were disease-free from 1-10 years after treatment. *Potter et al.* (16) reported on the treatment 28 pelvic recurrences (17 central recurrences and 11 side-wall recurrences) indicating a survival of 30% (40% for central recurrences and 23% for side-wall recurrences). *Krebs et al.* (17) described the results in 312 patients with carcinoma of the cervix treated with surgery alone: they observed 40 recurrences (13%), 11 of which were limited to the central pelvis; the 5-year salvage rate was 13%. *Webb et al.* (11) analyzed 104 recurrences after surgery alone for stage IB and found a 5-year survival rate of only 6%.

The typical treatment approach consists of a combination of external beam irradiation up to a total dose of 40 to 45 Gy followed by one or more intracavitary brachytherapy insertions (LDR or HDR) which may cover the vaginal vault or the entire length of the vagina depending on initial tumor volume (18). The mucosa of the vaginal vault can tolerate a total dose of radiation up to 140 Gy whereas the lower third of the vagina may receive up to 95 Gy without serious late side-effects (19). However, the efforts to improve local control by delivering high doses of radiation with intracavitary brachytherapy have been relatively disappointing in large recurrences of carcinoma of the cervix. In bulky central recurrences a better dose distribution may be obtained by means of an interstitial approach with total doses of 20-30 Gy (13, 20-21). If an exploratory laparotomy is performed, interstitial implants can be done at this time, either in the form of a permanent iodine-125 seed implant or as a temporarily removable after-loading iridium-192 implant. Although interstitial brachytherapy probably yields the most promising results in recurrent cervical cancer, severe complications may occur in up to 21% of patients with such an aggressive approach, mostly due to dose inhomogeneities. If the interstitial implant is not feasible, additional irradiation may be delivered with reduced portals up to a total dose of 65 Gy.

RECURRENCES AFTER RADIOTHERAPY ALONE OR AFTER COMBINED SURGERY-RADIOTHERAPY In patients treated with radical radiotherapy for carcinoma of the cervix, pelvic recurrences occur with increasing frequencies according to the stage of the disease: 2.2% in stage IB, 6.1% in stage IIA, 10.5% in stage IIB and 22.4 in stage III (22). Traditionally, the treatment approach of pelvic recurrences after radical radiotherapy has been surgery, either in the form of radical hysterectomy or of pelvic exenteration. Pelvic exenteration is reserved for extensive central failures, and apart from its high morbidity it warrants limited survival advantages (23). Furthermore, due to improved pelvic radiotherapy, recurrences confined to the central portion of the pelvis alone, potentially amenable to surgery are relatively limited in number, the majority of patients who relapse after radiotherapy having unresectable side-wall recurrences (13).

Historically, the local control rates achieved by reirradiation were rather discouraging and they were coupled with relatively high radiation-induced morbidity. *Murphy et al.* (24) reported a 5-year survival rate of approximately 20% in a group of 46 patients who underwent reirradiation for pelvic failure after radical radiotherapy; in the subgroup of patients who had disease limited to the vaginal vault the survival rate at 5 years was

47% (7/15) with a late complication rate of 50% which included two recto-vaginal fistulae. *Prasasvinichai and associates* (12) described a 17.6% 5-year survival rate in 51 patients with pelvic recurrences after previous radiotherapy alone (31 patients), pelvic exenteration (10 patients) or a combination of surgical debulking and irradiation (10 patients). *Thomas and associates* (25) reported a median survival of only 7 months in 242 patients with recurrent disease from cervical cancer of all stages treated with irradiation alone; all but one patient salvaged by hysterectomy died within 24 months of treatment. *Prempree et al.* (26) reported on eight patients with locally advanced cervix cancer who had been treated with radical radiotherapy with late recurrences: three survived disease-free at five years; of ten patients who recurred in the pelvis ten years or more after primary radiotherapy they found a 5-year survival rate of 60% (27). *Puthawala and associates* (28) treated 14 patients with pelvic recurrences who had been treated with exclusive radiotherapy with interstitial implants alone, and described a 50% (7/14) local control rate with good palliation of symptoms in up to 80% of cases; the incidence of mild side-effects (cystitis, proctitis) was in the order of 30%, but they also observed severe complications in 15% of cases (soft-tissue necrosis, rectal stricture, recto-vaginal fistula).

More recently, however, thanks to better irradiation techniques and to strict patient selection criteria, more promising results have been achieved, making reirradiation a viable treatment option. *Sommers and coworkers* (29) reported on the results of treatment of 376 patients with recurrent carcinoma of the uterine cervix; 91 patients were treated with external beam irradiation, occasionally combined with brachytherapy, or brachytherapy alone. Pelvic exenteration was attempted in 23 patients, only ten of whom were considered operable, but was completed in only seven. The 5-year survival rates after treatment for recurrence was 30% in patients treated with combined surgery and external beam irradiation, 12% in the patients treated with surgery alone and 4% in patients treated with external beam irradiation alone. Only 1% of untreated patients survived 5 years. These data suggest that although patients with pelvic recurrences who fail after initial treatment have indeed a poor prognosis, some patients with limited, resectable central disease, can be salvaged with additional aggressive therapy.

Of course, reirradiation must be undertaken with extreme caution. In particular, it is very important to assess the treatment technique previously used in every detail (beam energy, volume irradiated, total doses delivered with external beam, amount of small bowel in the treated volume, total dose delivered with brachytherapy). The time interval elapsed between the two treatments may also be taken into account, since it is postulated that some repair on the initial normal tissue damage may occur over a long span of time (30). At any rate, external beam irradiation can only be delivered to limited volumes up to a total dose in the 40-45 Gy range with standard fractionation, preferably using lateral portals. Intracavitary brachytherapy may be used as a form of boost, or occasionally as the only form of retreatment if the recurrence is confined to the vaginal vault.

COMBINED CHEMO-RADIATION Chemotherapy has not gained an established role in the management of recurrent cervical cancer for a number of reasons. Neoadjuvant and adjuvant randomized chemotherapy studies have failed to prove a benefit compared to irradiation alone in primary cervical cancer (31). Cytotoxic agents used in patients with recurrent cervical carcinoma have shown less than optimal efficacy. Moreover, other factors may complicate the administration of chemotherapuetic agents in recurrent cervical carcinoma, such as reduced pelvic perfusion, limited bone marrow reserve, and poor renal function due to compressive uretral obstruction. Prospective phase I/II studies to identify active agents in recurrent cervical carcinoma were conducted in the 1970s and showed cisplatin to be the single most active agent with response rates in the 15-20% range (32).

The use of chemotherapy as a radiation sensitizer is an attractive approach to enhance local control rates. Several small phase I/II studies of concurrent irradiation and chemotherapy have been performed, which have yielded variable response rates. Single-agent cisplatin regimens remain the mainstay of combined chemo-radiotherapy for recurrent cancer of the cervix, but no survival benefit has so far been proved (33). *Thomas et al.* (34) reported the results of salvage therapy in 17 patients with recurrent cervical cancer after primary surgery using 5-FU with or without mytomycin-C and radiation therapy. Forty-seven per cent (8/17) of the patients were alive and disease-free at 21-58 months, which could represent an improvement compared to irradiation alone. Further randomized studies are needed to confirm the added benefit of combined chemo-radiation with respect to radiation alone.

INTRAOPERATIVE RADIATION THERAPY (IORT) Intraoperative radiation therapy combines the effect of localized high-dose irradiation with the possibility of temporary removing or shielding of critical structures. Radiation is administered on the tumor bed in a single dose of 15-25 Gy with an electron beam from a dedicated linear accelerator at the end of the surgical procedure.

Few clinical studies have been reported on the use of IORT in pelvic recurrences from gynecologic malignancies and their results have been relatively disappointing especially for incompletely resected side-wall recurrences. The *French Intraoperative Group* (35-36) reported on 70 patients treated for recurrent gynecologic malignancies describing a local control rate of 21% and a 3-year survival rate of 8%. *Monge et al.* (37) reported on the use of IORT in 26 patients with recurrent gynecologic cancer, either after previous irradiation (group I) or surgery (group II). All patients were treated with a combination of surgical resection and IORT (10-25 Gy); patients belonging to group II (no previous irradiation) also received external beam radiotherapy. Local control rates were 33% and

77% respectively for the two groups. As may be expected the inability to deliver a full course of radiation treatment in previously irradiated patients considerably lowered the chances of local control. From these experiences it may be concluded that the most important prognostic factors predicting outcome of IORT treatments are: 1. central pelvic recurrences with no side-wall involvement, 2. complete surgical resection of the lesion, 3. full coverage of the surgical bed in the treated field, 4. no prior pelvic irradiation.

Although IORT does indeed offer some therapeutic advantages it is not devoid of sideeffects (38). In particular, peripheral nerve injury is known to occur when radiation is administered in large single fractions. According to *Shaw et al.* (39) peripheral lower extremity neuropathy is the most frequent IORT-associated toxicity (32%) and it is characterized by unilateral pain, numbness and weakness.

COMBINED OPERATIVE AND RADIOTHERAPEUTIC TREATMENT (CORT)

The Combined Operative and Radiotherapeutic Treatment (CORT) is a new treatment modality for patients with side-wall recurrences from gynecologic malignancies who have been previously irradiated. Extension of the tumor to the pelvic wall has traditionally been considered a contraindication for pelvic exenteration. Yet, the majority of patients with isolated side-wall recurrences present with a clinical history of adjuvant or radical pelvic irradiation and are therefore not amenable to a full course of irradiation. It has been argued that pelvic side-wall recurrences indicate metastatic systemic disease and that patients presenting with such recurrences probably would not be cured even if effective local control were feasible (40). However, there is increasing evidence that selected patients with side-wall recurrences may in fact benefit from an aggressive local treatment (41). To this aim *Höckel et al.* (41) developed a new radiosurgical treatment which involves perioperative brachytherapy either LDR or HDR. CORT is more radiobiologically sound than on large single fraction delivered by IORT.

The combined treatment consists of several steps:

- Pretreatment evaluation and patient selection
- Surgical exploration
- Tumor ablation with removal of infiltrated pelvic organs
- Implantation of guide tubes to cover the entire area of potential microscopic residual tumor surrounded by 2 cm margin
- Pelvic wall plasty with various flap techniques to create a protective distance between the tubes and the pelvic organs and to improve local microperfusion at the treated pelvic wall to reduce wound healing complications.
- Reconstruction of major pelvic functions (bladder, anorectum, vagina)
- Post-operative tumor-bed irradiation with remote afterloading brachytherapy (Iridium-192 HDR 48-54 Gy with 6 Gy fractions twice weekly)

Höckel et al. (42) have recently reported on the results of 48 patients treated with this approach. The 3-year and 5-year survival rates were 50% and 44% respectively. The most significant prognostic factors for tumor control were the presence of macroscopic residual tumor volume after debulking, young age (<40), size of recurrence disease (>4 cm). No treatment-related deaths have been reported. The overall severe complication rate is 33%. From the analysis of these preliminary data it appears that CORT is a feasible treatment modality in selected patients and that it can result in promising long-term survival advantage with acceptable morbidity.

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Perspectives of radiation therapy in the treatment of advanced stages (III and IV) of cervix carcinoma

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ABSTRACT Stage III and IV cervical carcinoma are normally treated with radiation therapy, alone or combined with chemotherapy. Results are far to be satisfactory (5-year survival varies from 30-45% for stage III, and from 18 to 25% for stage IV). Failure in the pelvis remains the most frequent cause of unsuccess. Efforts have been made in order to improve the local control of disease: radiosensitizers, hyperthermia, intraoperative approaches, and others. Results of different trials didn't show clearly benefit from this attempts. New perspectives in the field of radiation therapy for the cure of advanced stage cancer of the cervix could be derived from the recent developments in high technology. The possible role of hadrontherapy (charged particles such as protons and ions) and three dimensional conformal radiation therapy are discussed.

Key words cancer of cervix, hadrontherapy, 3-D conformal radiation therapy.

INTRODUCTION Incidence and mortality from cancer of the cervix have been decreasing steadily over the last three decades in the majority of the developed countries. This was considered to be due both to well-organised screening programs which can detect the disease before it comes symptomatic and attention in women for coexisting symptoms, such as vaginal discharge or bleeding, especially postcoital spotting. At present, the incidence varies internationally and interregionally in Europe, but the estimated total number of invasive cervical cancer in our continent is comprised from forty-five to fifty thousand per years (1); presentation of disease is early in 75% of these new cases, with only one fourth of women presenting with locally or far advanced disease (stage III and IV). These data have a considerable impact on the treatment outcome. As reported by literature data (2-5), the probability of cure is high in stage I (above 90%) and II (70-75%) cervical cancer, whereas for advanced stage III and IV 5-year survivals are disappointingly low at 30 to 45% and 18 to 25%, respectively. Although relapse due to early micrometastatic dissemination is a relevant pattern of failure in some locally controlled patients (in stage IIB through stage IV, the average incidence of distant metastases is about 20%), most of failure occurs at primary site. The magnitude of the problem can be appreciated with the high rate of local recurrence or persistent disease of 37 to 45% in stage III and 71 to 78% in stage IV. Therefore, there is the need to develop new and effective treatment strategies for improving local control in these groups of patients with advanced stage cervical cancer.

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THE ROLE OF RADIATION THERAPY Patients with stage III and IV (and often with IIB stage) cervical cancer are normally treated with radiation therapy alone. Standard external beam irradiation is employed to treat the whole pelvis (or more extended field in case of metastatic involvement of the para-aortic lymph nodes), with intracavitary brachytherapy (and sometimes interstitial implant) reserved for supplementing the dose to the central disease.

The effectiveness of irradiation for these patients can be correlated to the volume of tumor in pelvis; for example, patients with stage IIIB are more likely to have a local failure if the disease is extended to bilateral pelvic sidewall compared with those with unilateral involvement. *Kramer et al.* (6) reported on 48 patients with stage IV cancer a 5-year survival of 46% for cases with minimal parametrial involvement and of 5% for those with more extensive disease. In total only 9 patients survived without recurrence. The radiotherapeutic regimen was quite aggressive (30 to 45 Gy to the whole pelvis with an additional parametrial dose of 10-15 Gy, combined with one or two intracavitary insertions for further 30 to 50 Gy to the Point A) and a high rate of serious complications was observed: 22% with 5 vesicovaginal fistulas. *Perez et al.* (7) showed that increasing the dose to the lateral parametria to more than 6750 cGy in stage IB disease still produced a parametrial failure rate of 30% with a considerable increase in

complications, but an improved tumor control was observed with higher level of total dose (80-90 Gy to Point A) in more advanced stages, IIB and III (8).

The positive correlation of the higher total dose delivered to the central disease with the greater tumour control rate is confirmed from other authors which employed brachytherapy as a part of the entire treatment. Interstitial implants are useful to boost residual infiltration of proximal and even distal parametria, especially when residual disease extends posteriorly to the uterosacral ligaments or when there is a narrow vaginal vault and/or no possibility to probe the uterine cervix. Excellent local control can be obtained (9-10), but it is unlikely that controlled studies on this method can be carried out since the extreme selection of clinical indications. Intracavitary brachytherapy can be performed at various dose-rate; LDR (low dose-rate) is usually delivered in one or more continuous applications after the completion of external beam irradiation, whereas HDR (high dose-rate) can be fractionated in four to eight applications of few minutes each, given after or also concurrently the course of external radiation therapy, in the attempt to reduce, by the shortening of the overall treatment time, the tumor cell repopulation. Because of important consequence of the dose-rate variations according to the proliferation rates of different tumors and some uncertainties in selection of patients, ideal timing, fractionation, prescription point and so on, it is very difficult at present to compare the results obtained with the two different brachytherapy methods. For patients with stage III cancer, data of LDR results (5-year survival of 51.1%) from the French Cooperative Group (4) favourable compared with HDR results (47.2%) from the *Orton* (11) survey, but also with LDR results (37.4%) from FIGO (5), confirming that the effectiveness is strictly correlated to the treatment quality. Improvements in therapeutic ratios could be derived from PDR (pulsed dose-rate), a technique in which a continuos LDR treatment is replaced with a series of short (ten minutes) HDR irradiations given every hours and taking the same overall time (12).

The limited success in controlling advanced but localised cervical disease with conventional external beam irradiation have stimulated a search for improved methods to accomplish a permanent control of the primary tumour at the initial therapeutic attempt. The trial of hyperbaric oxygen (13) as a radiation sensitiser had shown some decrease in the local recurrence rate of carcinoma of the cervix; however, other reports have also indicated increased normal tissue complications (14). The RTOG trial (15) randomising misonidazole and radiation versus radiation alone was not only unsuccessful in terms of survival and control rates, but there was reported a significant complication caused by the drug's neurotoxicity. In a phase III trial on advanced stage IIB and III cervical cancers treated with combined external beam irradiation and brachytherapy with or without pimonidazole (a second generation 2-nitroimidazole), patients who received the biochemical modifiers had statistically significantly lower local control, disease free and overall survivals (16). The reason for the poor outcome in the sensitiser group of patients is not known with certainty, although there is speculation that pimonidazolo may have decreased tumor perfusion. Results of non-randomised trials using combined radiotherapy and hyperthermia seemed encouraging but far from satisfactory (17). Also the use of a unconventional radioisotope, such as the releasing neutrons Californium 252, didn't show significant benefit on either local control or survival (18). *Calvo* (19) investigated the use of IORT in 24 patients; local control of 80-84% was observed, with the primary complications being pelvic pain.

Chemotherapeutic agents, including 5-FU, cisplatin, and mitomycin-C, individually or combined, have response rates between 20 and 50%. However, these drugs used as concomitant infusion with irradiation show a radiosensitising effect that produces a considerable enhanced local response rate in locally advanced disease. *Princess Margaret Hospital* (20) using 5-FU and mitomycin-C in advanced disease reported a complete response rate of 74%, and at 15 months 59% of patients remained disease free. At Fresno Community Hospital, *John et al* (21), using continuous infusion of 5-FU and radiotherapy and cisplatin reported a 100% complete response rate in a small series of cases, and with a median follow-up of 28 months 80% were alive and free of disease without a significant increase in toxicity. *Ludgate et al* (22) have reported on a series of 38 patients with bulky stage IIB, IIIB, and IV treated with mitomycin-C, 5-FU infusion and concomitant external irradiation. A complete response rate of 76% for the entire group was obtained 3 months after completion of therapy with an overall 3-year survival of 55%. The 3-year survival rate of 79% for stage II bulky disease patients was significantly better than 38% obtained with conventional therapy. *Piver et al.* (23) at Rosweel Park have conducted several trials evaluating hydroxyurea radiosensitisation. In one of these studies patients with stage IIIB were randomised to receive external and intracavitary radiotherapy with or without hydroxyurea. The estimated 5-year disease free survival was 54% for combined treatment and 18% in the control arm. Many recent trials used cisplatinum with or without 5-FU and reported encouraging results (24-25), however, mature results from randomised comparisons are necessary to establish the efficacy of these approach.

NEW PERSPECTIVES IN RADIATION THERAPY Analysis of the causes for local failure after radiation therapy require considerations of multiple biological and treatment-related factors. The application of new high-precision radiation therapy, together with improved staging and better assessment of tumor characteristic (DNA ploidy, proliferative activity, individual radiosensitivity) is expected to improve tumor control probabilities. Current studies currently under way have been designed to test the effect of dose on the probability of local control. Research efforts to exploit modern technology in order to improve the technical aspects of radiation treatment can include attempts to reduce the irradiated volume; from a theoretical point of view, reduction in the volume of normal tissue irradiated, besides

diminishing the likelihood of treatment-related morbidity, allow a higher dose to be given to the tumor with relative safety, thereby increasing the probability of achieving the desired therapeutic goal. Strategies aimed at realising smaller irradiated volumes in the patient are the use of heavy charged particles (hadrontherapy) or of three-dimensional (3D) conformal photon beam radiotherapy.

HADRONTHERAPY Today, hadrontherapy is delivered with neutron, proton and heavier light ion, and negative pions beams. These modalities bring unique clinical potentialities with them thanks to the fact that the physical characteristics of the various hadron radiations deviate markedly and favourably from those of "conventional" radiations. In particular, high energy (200 MeV or more) proton beam combine the most attractive properties of therapeutic electron and photon beams, such as suitable penetrability, little scattering and an almost definite range of penetration. In addition, the relative absorbed dose shows a useful increase with the depth. By using techniques based on variation of the depth of penetration during irradiation, the dose distribution can be tailored to fit almost any chosen target structure in the body. The impressive clinical successes achieved by the Massachusetts General Hospital and Loma Linda University in the proton therapy program continue to fuel the burgeoning interest through-out the world in the treatment of human malignancies. To date, several projects exist in Europe to construct centres for the medical use of charged particles; an Hadrotherapy Project was also initiated in Italy in 1991 (TERA Project). It is considered that about six thousand Italian patients could really profit from proton treatments (26). The pathologies characterised by a potential indication have been subdivided into four categories. Category A includes tumours (uveal melanomas, sarcoma of the base of the skull and of spinal chord, etc.) which are characterised by their closeness to highly critical structure. The list of pathologies belonging to Category B comprises tumours with low radiosensitivity and a prevalent local evolution (retroperitoneal sarcomas, adenocarcinomas of the prostate, salivary glands, thyroid, etc.). Category C includes tumours for which the main indication for protons is the boost on a restricted volume: head and neck cancers, low-grade gliomas, etc. Category D includes locally advanced tumours with very unfavourable prognosis for which palliation with conventional beams can be unsatisfactory for too high level of side effects. Carcinoma of the cervix (stage IIB bulky and stage III) is included in the Category B. The total number of expected cases per year in Italy is comprised between 440 and 530, of which the 30% suitable for protons. In Europe the number of patients eligible for proton beams should be of 6300 per year. In a limited series of patients (23 cases) with cervical cancer treated in Japan, at Tsukuba University, a local control rate of 87% was observed, confirming the effectiveness of this approach. Patients with para-aortic lymph node metastases or pelvic recurrence after previous irradiation are included in the Category D (palliative intent). The total number of expected cases per year has not yet been defined.

THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) 3D-CRT is a mode of high precision radiotherapy. It is based on treatment designs which shape the isosurface of a given radiation dose to accurately conform the anatomic boundaries of the tumour in its entire three-dimensional configuration (27). The improved tumour coverage and the increased tumour dose are likely to improve local control, although this benefit must be demonstrated. Very encouraging clinical results have been observed in the treatment of prostate carcinoma (28). Few data exist on gynecologic cancers. To date much of the technology required for 3D-CRT is in an advanced state of development. CT and MRI, as single modality or by fusing different images, furnish detailed 3D anatomy for a specific patient that can be incorporated into radiation therapy planning systems. Treatment delivery has improved with the multileaf collimator, dynamic wedge, computer control of treatment parameters, and better immobilization devices. On-line portal imaging devices ensure verification of the quality of treatment. Further developments are necessary in the field of algorithms to integrate the different parts of the system (CT/MRI, planning workstation, multileaf collimator and portal imaging) in order to optimise the treatment and to ensure safety and quality to the patient.

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Neoadjuvant chemotherapy in squamous carcinoma of the uterine cervix

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INTRODUCTION In spite of the progress reached with early detection and screening since the introduction of the Papanicolau smear, in many countries of the world its incidence is very common, representing one of the most frequent sites of female malignancy. Furthermore diagnosis is often made in advanced stages of the disease. Survival rates using radiotherapy, the standard treatment for locally advanced squamous carcinoma of the cervix uteri, have remained almost unchanged in the last decades. The same occurred with surgery, the standard treatment for earlier stages of the disease. For these reasons, new strategies are being tried in several oncologic centers around the world.

One new approach is the concurrent use of chemotherapy and radiation therapy, so-called chemoradiation. Scientifically, this is based on the inhibition of clones of cells that may be resistant to radiotherapy. Furthermore, in high-risk patients, it is desirable not only to achieve adequate regional control but also to exert a systemic effect because such patients frequently have disease outside the standard irradiation field (1-2).

Another therapeutic strategy is the administration of chemotherapy before any other treatment in order to reduce the volume and the extent of the disease. This would allow radiation of the tumor under more favorable conditions or make surgical treatment possible in clinically inoperable patients (3-5). Many arguments have been used to justify or to question the use of neoadjuvant chemotherapy. Among the former can be mentioned the decrease in tumor volume and extent of disease spread, the capacity to tailor the adjuvant chemotherapy according to the primary tumor response and the treatment of the micrometastases. Among the disadvantages are the delay in the initiation of curative treatment, the development of radioresistant cell clones, and the cross resistance with radiotherapy. In larger tumors, two problems have to be addressed: the management of the primary tumor and the management of the regional lymph nodes and subclinical distant spread. Concerning the primary tumor, the possibility of obtaining a complete response with radiotherapy is relatively low and, with chemotherapy alone, almost nil. Surgery appears to be the best option to improve survival in these patients after reduction of tumor with chemotherapy. In our experience, in the great majority of these cases, it is possible to obtain specimens with free surgical margins. With these factors in mind a multiple randomized study with neoadjuvant chemotherapy was initiated in the Gynecologic Oncology Unit of Buenos Aires University. Our goal was to determine if this therapeutic strategy could increase survival in patients with bulky stage IB tumors and in locally advanced cervical carcinoma and, if such was the case, whether radiation therapy or surgery should be preferred definitive therapy. The neoadjuvant chemotherapy scheme used was composed of cisplatinum 50 mg/m^2 bolus day 1, vincristine 1 mg/m^2 bolus day 1, and bleomycin 25 mg/m^2 days 1 to 3 (6 hr continous infusion). Three courses were administered at 10 days interval.

NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY Up tp now, pilot phase II trials have shown that neoadjuvant chemotherapy followed by radiotherapy is feasible, with no major toxicity. However, these trials were not informative as to any influence on survival by neoadjuvant chemotherapy. Unfortunately, randomized trials on neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced cervical carcinoma proved disappointing, especially in terms of showing a survival benefit. In fact, only two of the phase III trials have shown improved survival. The one of *Park* (7) and the other from our *Unit* (6). The majority of these phase III trials can be criticized in terms of selection of patients, number of cases in each arm, and the neoadjuvant chemotherapeutic scheme utilized. The critics and comments to the different trials (8-13) can be found in our last paper on the subject (14). For these reasons, it was previously not possible to firmly establish whether or not neoadjuvant platinum based chemotherapy followed by radiotherapy is more effective than radiotherapy alone in the treatment of cervical carcinoma. In our experience, chemotherapy with platinum compounds at 10-day intervals in conjunction with high-doses of bleomycin

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produces better overall survival and disease free interval in stage IIIB disease, mainly in patients with large tumors. In stage IIIB tumors of small volume and in IIB disease no significant differences were obtained, altough in the latter, a marked reduction in pelvic recurrences was observed.

It can be said, that in all studies in which neoadjuvant chemotherapy followed by radiotherapy was used with appropiate drugs and adequate doses, a larger number of complete remissions was obtained, as compared to treatment with radiation alone. This advantage did not result in improved survival in stage IIIB patients with large tumors, except in our protocol. Similar outcomes have been observed, however, in patients with locally advanced head and neck cancer. Explanation for why one may see improved responses with neoadjuvant chemotherapy, but not see improved survival, cannot be given with certainty, but it has been suggested that chemotherapy could lead to an accelerated regrowth of surviving clones of cells, thus lessening the effect of subsequent radiotherapy (15). Another possibility is the development of cross-resistance to certain chemotherapy agents and radiotherapy regimes.

An interesting observation that could provide a clue to the future treatment of patients with advanced cervical cancer is that the responders to neoadjuvant chemotherapy have better local control of the disease. Therefore, response to chemotherapy could represent a good predictor of radiosensitivity, and in patients with a poor response to chemotherapy, surgery might be the better second-line treatment. In our study, a paradoxical finding was made, which contradicted the results of *Tattersall et al.* (12), consisting in an unusual high incidence of distant metastases in patients who had a good response to chemotherapy. This observation could not be satisfactorily explained because a similar increase in distant metastases was not found in the group treated with chemotherapy plus surgery. It is not known if this phenomenon is a change in the natural history of advanced cervical carcinoma due to treatment or an undesired effect of neoadjuvant chemotherapy due to immunosupression and the fact that radiotherapy does not produce tumor destruction or removal as quickly as surgery. Recent studies in patients with squamous cervical cancer have shown that neoadjuvant chemotherapy with cisplatinum and bleomycin reduces natural killer activity (16). Although polychemotherapy reduces tumor spread, its antineoplastic action can be affected by this decrease immune reactivity,which could help explain the results observed in our study. It can be concluded that many of the theoretical difficulties of neoadjuvant chemotherapy could be avoided using surgery as a second-line treatment.

CHEMOTHERAPY FOLLOWED BY SURGERY Two are the circumstances to use neoadjuvant chemotherapy followed by surgery: a) for locally advanced stages IIB and III, for which its use may be justified because it allows greater operability and thus a greater possibility of cure for these patients (17-19); and b) for patients with bulky clinically resectable stage IB. Due to their large volume, these large stage IB cancers are frequently understaged so when the exploratory laparotomy is performed, the tumor is unresectable due to parametrial extension, extension through the cervix beneath the bladder or unresectable lymph node metastases. Radiotherapy has been the treatment of choice for these cases; however, due to their volume, they have hypoxic cell population that may reduce radiosensitivity. Another problem for radiotherapy is the extension to the lower part of the uterine cavity with the corresponding dosimetric problem. To avoid the central recurrence which is frequently observed in these cases, it has been proposed that treatment be completed with a simple extrafascial hysterectomy after radiotherapy (20). Later studies have not supported such a hypothesis (21-22) and so far the GOG trial 71, which randomizes patients to radiation alone or radiation followed by hysterectomy, has not shown benefit in overall or disease free survival or local control of the disease. Other authors, including *Bloss et al.* (23) propose radical surgery for these cases and obtain the same results as with radiotherapy in terms of survival and pelvic recurrences.

In our stage IB trial (102 patients in the neoadjuvant group and 103 in the control arm) there was no benefit in survival or in pelvic recurrences in tumors with a diameter of less than 4 cm (stage IB1). The results were 89% overall survival in the control versus 91% in the neoadjuvant group. However statistically significant differences were achieved in tumors with a diameter larger than 4 cm (stage IB2) in overall and disease free survival. The results were 64% overall survival in the control versus 83% in the neoadjuvant group. This was due to the fact that, in these cases, all of the patients in the neoadjuvant group were surgically resected (61 cases), while only 85% could be resected in the control group (48 of 56 cases). The survival rate of the eight patients with stage IB2, that were surgically unresectable, was significatly worse than that for patients that were surgically resectable. Also statistically significant differences in free disease survival were observed in surgically resected bulky tumors. In all of the cases a significant decrease in the number of pelvic failures was achieved. This was due probably to the downstaging produced by the use of induction therapy. In another randomized trial reported by *Lee et al.* (24) the 3,5 year disease-free survival rate of stages IB and IIB patients was 81% in the chemotherapy group compared to 69% in the surgery arm alone. With these results it is clear that neoadjuvant chemotherapy associated with surgery is a valid and valuable alternative for patients with bulky IB cervical cancer. *(Table 1.)*

Among stage IIB patient an increase in survival was observed in those treated with neoadjuvant chemotherapy plus surgery (72%) versus patients treated with chemotherapy plus radiotherapy (59%), and both controls (53% in the surgery control group and 50% in the radiotherapy control group). This fact was due to a reduction in pelvic recurrences, especially in the surgical group. Another remarkable observation was the increased operability of patients treated with chemotherapy (68 of 79,89%) compared with the control group treated with surgery alone (50 of 75,67%).

Table 1. Current therapeutic alternatives in stage IB2 cervical cancer

Treatment	Number of Patients	5-Year survival (%)	Pelvic recurrence (%)	Distant recurrence (%)	Selection
GOG trial 71					
—RT	124	60	23	11	Neg.nodes
—RT + Tot.Hyst	132	66	23	11	Neg.nodes
DiSaia WM + RT	82	68	28.5	4.7	Clinically
Buenos Aires trial					
—WM + RT	56	64	23	12	Unselected
—NC + WM + RT	61	84	6.5	6.5	Unselected

RT Radiotherapy WM Wertheim-Meigs operation NC Neoadjuvant chemotherapy

Similar conclusions were obtained in stage IIIB patients, in which surgery had better results. In this trial it was not possible to demonstrate a clear-cut advantage of the combination of chemotherapy and surgery versus chemotherapy and radiotherapy. So, perhaps the question that we have entertained for a long time concerning patients with cervical cancer and the possible improved operability could now be answered affirmativelly.

THE LIMITING FACTORS OF NEOADJUVANT CHEMOTHERAPY

Tumor volume in advanced stages has attracted our interest since 1987 (25), as well as that of other researchers (26). In our experience response to neoadjuvant chemotherapy is excellent in tumors with diameter up to 5 cm, but larger tumors do not respond as well. Tumors with diameters larger that 9 to 10 cm respond poorly to neoadjuvant chemotherapy. This is a limiting factor for surgery since in most cases, free surgical margins can not be obtained. Although controversial, radiotherapy following chemotherapy could be curative treatment for these patients; in our randomized trial in stage IIIB with tumors larger than 5 cm in diameter radiotherapy achieved improved survival with respect to the control group, but that difference was not statistically significant.

Hydronephrosis may be a limiting factor especially when associated with bilateral sidewall parametrial infiltration. When it occurs the response and survival diminish significantly.

The presence of **lymph node metastases** has a great impact on survival of patients treated with neoadjuvant chemotherapy. In this respect the data from our studies as well as that from the literature are controversial. Phase II trials showed that the incidence of nodal metastases diminished in patients treated with neoadjuvant chemotherapy. This has been also confirmed by randomized protocols (26-27), but the presence of nodal metastases after neoadjuvant chemotherapy constitutes a very poor prognostic factor. *Zanetta et al.* (28) achieved a 35% complete response rate of nodal metatstases with neoadjuvant chemotherapy, as well as a survival rate of 66% in stage IB to IIIB patients with previous lymph nodes metastases. In the case of persistance of nodal metastases, the survival was 27.5%, which is the same as the result obtained in our randomized experience with stage IIIB patients.

CONCLUSIONS We believe that neoadjuvant chemotherapy can be used as an alternative treatment in locally advanced tumors or large localized tumors without nodal involvement. It is necessary to use high doses of platinum and bleomycin to achieve a good tumor response and a satisfactory downstaging. Surgical treatment after neoadjuvant chemotherapy appears to be the most appealing option.

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Contramal

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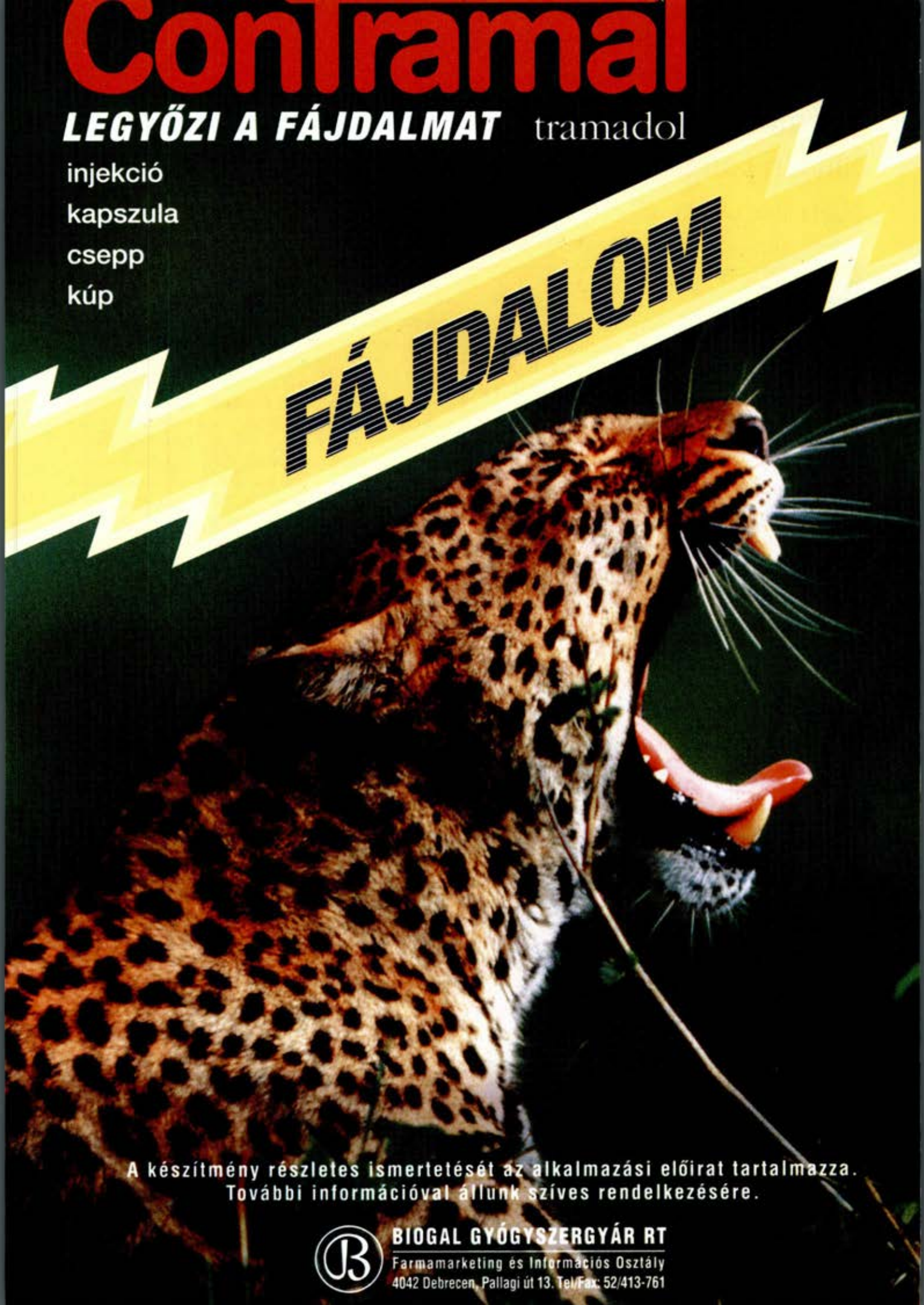

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Chemotherapy prior to radical surgery in cervical cancer: can it be justified?

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INTRODUCTION Promising results with the use of neoadjuvant chemotherapy prior to radical surgery in the treatment of cervical cancer have been repeatedly published over the last 15 years. In spite of the efforts invested into studying the possible role of this treatment modality, (as it was declared recently) has not been clarified: "Its value will not be determined without properly conducted large randomized studies" (1). Why did *Elliott* (1) mention a "proper" and a "large" study? He himself is one who has reported his own results about the question. Did he ever carry out an improper trial? Properly conducted "normal size" studies might not be enough to clarify the question? In my presentation I tried to examine this problem from the side of the radical surgeon.

CHEMOTHERAPY REGIMEN Although the use of Platinum containing chemotherapy regimens in previously not treated cervical cancer has proven to be effective in about 50-100% of cases, and complete or partial response to chemotherapy will enable surgeons to operate on previously technically inoperable patients, significant increase in survival has yet to be proven. *Sardi et al.* (2) in their recent publication suggested to revise the chemotherapeutic scheme used in some of the trials published, and it might also be questioned, whether the high toxicity caused by the cytostatic treatment (probably due to the heterogeneity of the sampling), conspired against the results. Other studies were criticized by the same author because of bias in the selection of cases. As it has also been stated by *Sardi et al.* (2): "We are convinced that in a neoadjuvant chemotherapy trial it is essential to administer the cytostatic scheme at the highest tolerable dose to produce the greatest possible response and thus improve the classical treatment. That is why our scheme is based on the administration of a normal dose of cisplatin repeated at short intervals, and a high dose of bleomycin, to achieve the above mentioned objectives."

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HOW THE SURGICAL PROCEDURE WILL BE INFLUENCED BY HIGHEST TOLERABLE DOSE OF CHEMOTHERAPY? Since radical surgery is a decisive part of the treatment, the other fundamental question is: the limited possibility to study the effectiveness of surgical treatment modalities. To my experience, the surgical situation in patients, where the previously unresectable tumor was dominated by chemotherapy, is different from those, found in primarily operable cases. In this sense neoadjuvant chemotherapy in cervical cancer in stage IIB and up, will mean a new surgical challenge, with new technical problems, complications, indications and contraindications. Can this surgical task be studied?

IS IT POSSIBLE TO STUDY NEW SURGICAL APPROACHES PROPERLY? "Classic innovations in medicine usually have been based on a medical (not surgical) model. A new medication is refined in the chemistry laboratory and tried first in vitro (i.e. non-living experiments). It is then tested in the animal laboratory. If it still appears safe, internal review board approval is sought for a clinical trial. When this approval is obtained, the protocol is put into place, with frequent statistical analysis and oversight for possible unexpected complications. The study is best designed as a prospective, randomized study with matched control subjects. The results are then published in peer-review literature to be duplicated or disputed by others before general clinical distribution of a drug is considered. Statistical significance is generally required for a drug to be considered effective. The honest, open sharing of information has been the key element in medical progress over the centuries."

Seldom has this pattern been followed in surgical innovation. I could not find a single publication dealing with the problems of radical surgery followed by chemotherapy in previously inoperable cervical cancer patients. This might be due to the nature of surgical innovation. Let us try to look at the question in general:

Early surgeons became famous for innovative methods, but few followed any scientific process in their careers. The point should be obvious. The haphazard application of new surgical techniques without prior scientific thought and without the accurate data collected to verify results does not enhance progress, and may actually impede it. In fact, although there

are many barriers to the use of an absolutely pure scientific method in surgical innovation, basic scientific concerns cannot be forgotten totally without sacrificing both patient safety and medical progress. In general, because a procedure was done "this way" in the past does not mean it should be continued. Changes in indication mandate constant reconsideration of common procedures.

On the other hand unlike medicine, surgery is an acute activity that often demands instant innovation. What "works" in a particular patient may not be what was scheduled. Although anatomic variations and disease processes may foil the best prospective plans of any surgeon, they must not prevent retrospective review. The only way to study such "essential" innovations is by a retrospective study of procedures found to be useful in similar clinical settings. How different surgeons have managed similar clinical situations is educational to other surgeons and ultimately helpful to patients. If we accept this way of thinking, we might accept the retrospective analysis of data collected at this new field of radical surgery.

IS IT POSSIBLE AT ALL TO CARRY OUT PROPERLY CONDUCTED LARGE RANDOMIZED SURGICAL STUDIES? This type of study is the gold standard of clinical research. Although it is readily accomplished in medicine, however, it is difficult to accomplish in surgery. The reasons are obvious. If different patient groups are used, was the surgeon the same in every case? Was the technique the same in every operation? Much must be accomplished before surgical studies are even feasible. For example, standardization of diagnostic terminology (properly measured tumor regression and operative finding). No multicentric comparisons will ever be accomplished without these first steps. The same is true for the establishment of long-term follow-up procedures, the mandatory reporting of complications, and the full description of procedures written in a way that allows peer replication and review. These procedures are more difficult for surgical procedures than for therapeutic trials of medications, especially in complex treatment modalities, where surgical opportunities and problems are created by the neoadjuvant part of the treatment.

Because of the acute nature of surgery, the necessity of innovation at times to perform surgery successfully, and the inherent difficulties in making the pure scientific method adaptable to surgery, it may not be possible to put every procedure on an Institutional Review Board protocol, and every detail, that might be considered as innovation could not be discussed by scientific boards. Nevertheless, certain procedures must become routine, if neoadjuvant chemotherapy induced tumor regression will induce surgical interventions.

OUR EXPERIENCE During the last 4 years a phase II clinical trial was initiated at the Gynaecological Oncology Service of Saint Stephen Hospital Budapest. In a homogenous stage IIB cervical cancer group of patients neoadjuvant chemotherapy (using the chemotherapeutic regime published by *Dottino et al.* (3) followed by radical hysterectomy was planned, with the aim to assess the acceptability, unsuspected complications, possible survival benefit (compared to historical controls) of the procedure. 70 patients were enrolled into the trial. On day one and 21 the same dose of chemotherapy (cisplatin 50 mg/m^2, vincristin 1 mg/m^2, mitomycin-C 10 mg/m^2 and, bleomycin 15 mg) was given. Radical surgery was planned for the 35th day of treatment. Clinical response to chemotherapy was not different from those reported in the literature. (Overall response rate was 70%, with a complete response rate of 20%.) 4 patients out of 70 progressed during treatment, and surgery was abandoned in these cases. The trial is in progress, and survival data were too early to evaluate. Some surgical conclusions however can be withdrawn from the experience of these cases.

CONCLUSIONS The conclusions are typical for the surgical clinical trials in general, demonstrating the difficulties of interpreting such results.

1. Pathologic complete response was found in 10 patients, where clinical response was detected as partial. We must point out, that intraoperative finding was not more accurate in predicting pathologic complete response, than the clinical examination prior to surgery. Scary tissue adherent to the large vessels, pelvic sidewall, sciatic nerves was a frequent intraoperative finding even in pathologically negative cases.

2. Scary adherent tissue from the obturator fossa in about 20% of cases was not possible to remove completely without the removal of the intrapelvic branches of the hypogastric artery and vein. This procedure did increase the operating time, bloodloss and the number of patients with the need of intensive care unit.

3. Bilateral removal of the hypogastric vessels is possible without significant increase of the complication rate, compared to the unilateral procedure.

4. Bilateral hypogastric vessel removal plus the ligation of the inferior mesenteric artery at paraaortic block dissection produced transient hypoxic colitis, with diarrhea, pelvic pain and fever in one of our patients. This symptom lasted 2-3 weeks. We do not recommend the simultaneous ligation of these three arteries.

5. Wertheim patients following chemotherapy tolerated less bloodloss, and needed more blood transfusion than not pretreated patients. (However we must bear in mind, that the historical control group of patients were not selected from the same stage of the disease.)

6. Partial or total removal of urinary bladder and ureteric resection, with some form of reconstruction might become

necessary if this treatment modality is used. In our experience the need for such procedure is not fully forseeable.

In conclusion: the retrospective evaluation of radical surgical procedures, and the refinement of techniques based upon these examinations is mandatory.

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The role of adjuvant radiation therapy in the management of ovarian malignancies

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INTRODUCTION In considering the role of radiotherapy as an adjuvant to surgery or chemotherapy it is necessary to group ovarian malignancies as epithelial carcinoma, germ-cell tumours, sex-cord stromal tumours and very rare conditions such as sarcoma or lymphoma of the ovary.

EPITHELIAL CARCINOMA By far the largest group of ovarian malignancies is epithelial carcinoma. These tumours range from those with a very good prognosis, such as borderline carcinoma of the ovary, to those with a poor prognosis, such as serous cystadenocarcinoma and the relative proportions of these different prognostic types in reported series can make comparison difficult. However, by far the most important prognostic factor is the stage of disease and the bulk of tumour remaining in the patient after surgery. In reviewing reported series it becomes apparent that the surgical procedures used to stage the patient, the taking of peritoneal washings, sub-diaphragmatic and nodal biopsies vary, as does the amount of 'de-bulking' achieved. This variation in the accuracy of staging may have a major impact on the interpretation of results just as the effectiveness of 'de-bulking' does.

Radiotherapy may be used as an adjuvant to surgery alone in patients in whom de-bulking has been thorough, or it may be used as adjuvant 'consolidation' therapy in responding patients following surgery and chemotherapy.

Although the FIGO staging system defines four stages and ten substages of disease, the biggest break in prognosis occurs between there being no peritoneal involvement (Stage Ia and Ib) and there being tumour on the peritoneum or in ascites. Once the peritoneum is involved the whole of that membrane both pelvic and abdominal, must be considered to be at risk. Therefore, radiotherapy to the pelvis alone is inappropriate and if radiotherapy is to be used a technique should be used that can treat the entire peritoneum. To achieve this radiotherapy may be delivered by external beam treatment or by the intraperitoneal instillation of a radioisotope.

Experience has shown that radiotherapy is a valuable palliative treatment for localised ovarian tumour masses, especially those causing pain or bleeding in the pelvis, and lasting measurable responses can be obtained. However, the radiation dose that can be delivered to the pelvis (60Gy) is considerably higher than that tolerated by the upper abdominal organs such as the kidney (20Gy), the liver (30Gy) and the small bowel (45Gy). This limitation on dose in the upper abdomen is such that there can be hope of erradicating only the most minimal microscopic burden of tumour at this site unless the radiation can be targetted by using a radioisotope attached to a monoclonal antibody, a technique which is still very much at the research stage (1).

EXTERNAL BEAM THERAPY FOLLOWING SURGERY The earliest and best reported experience in using external beam radiotherapy following surgery was that of the Princess Margaret Hospital, Toronto. Their first finding was of the lack of value of pelvic radiotherapy alone and they recommended that if radiotherapy was to be used then the target volume should include the whole of the abdomen and pelvis to encompass the entire peritoneal surface (2).

Their second finding was that radiotherapy was ineffective if the abdominal disease was anything more than microscopic and if the residual disease in the pelvis was >2cm in diameter.

Their third finding was that patients could be divided into low, intermediate and high risk groups on the basis of the tumour histology, the residual disease and the stage of disease. Abdominopelvic radiotherapy appeared to benefit those in the intermediate group, as those in the low risk group did well with no adjuvant treatment and those in the high risk group fared badly whatever the treatment (3).

In this group of patients with intermediate risk factors radiotherapy appeared to be more effective than chemotherapy with chlorambucil. This finding is interesting but is really of

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historical interest only as modern chemotherapy would include a platinum compound or a taxane or both.

Their fifth finding was that the 'moving strip' technique, which they used initially and which delivered a higher biological dose to the abdomen, was no more effective than an open-field technique and was associated with a higher complication rate. In addition this technique took ten weeks and was very resource-intensive.

In conclusion it has been shown that abdomino-pelvic radiotherapy can cure some cases of ovarian carcinoma. However, these must be of favourable histology and with microscopic disease only in the abdomen and small deposits only in the pelvis. The radiotherapy is very limited by normal tissue tolerance and may be tolerated badly by the patient either acutely or in terms of late damage, to the bowel in particular. It has not yet been clearly shown that in this group of patients radiotherapy is superior to modern chemotherapy.

EXTERNAL RADIOTHERAPY AS CONSOLIDATION AFTER SURGERY AND CHEMOTHERAPY Much the same conclusion can be reached when looking at the role of radiotherapy after chemotherapy following initial debulking surgery. Not only is it important that only microscopic disease remains after chemotherapy but the initial pre-chemotherapy bulk of disease is also important. Moreover, secondary debulking after chemotherapy seems not to benefit prognosis (4).

In these patients there are two further problems. The first is to define the response to chemotherapy. If the same criteria are adopted as for patients receiving radiotherapy after surgery alone then the response assessment should be at laparotomy taking the same biopsies as would be taken for initial staging, a process that worsens the morbidity of radiotherapy. The second problem is that the risk of radiotherapy-induced haemotological toxicity is higher in patients who have received chemotherapy than in those who have not.

In some series a group of patients can be identified who may benefit from post-chemotherapy radiotherapy (5). It comprises of those patients who underwent complete or near complete initial debulking and who then showed a complete clinical response to chemotherapy with either no residual disease or microscopic disease only. These patients should not have undergone more than six cycles of chemotherapy or extensive secondary surgery. In order to avoid major bowel and haematological toxicity the radiation dose to the abdomen should not exceed 22.5-25Gy and that to the pelvis 45Gy. However, in other series no benefit to post-chemotherapy radiotherapy has been shown (6).

Finally, whilst adjuvant abdomino-pelvic radiotherapy may benefit this small group of patients, the impact of more effective second-line chemotherapy on survival is not yet known.

INTRAPERITONEAL RADIOTHERAPY Intraperitoneal instillation of colloids of radioactive gold and of phosphorous have been used sporadically for many years. Because of the very superficial penetration of the radiation from these substances only microscopic disease or nodules of less than a few millimetres could be treated. In addition, whilst external radiotherapy treats the abdominopelvic lymph nodes in addition to the peritoneum, radioactive instillations provide only a small dose to lymph nodes. Radioactive gold emits gamma rays in addition to beta rays and is therefore more hazardous to staff and more toxic to the patient. As a consequence radioactive phosphorous is the isotope that is used.

There are no randomised studies of radioactive phosphorous versus no adjuvant treatment in early stage disease. The only randomised studies have compared radioactive phosphorous to chemotherapy and, to date, no difference is seen between these two treatments in effectiveness but the toxicity of radioactive phosphorous to the bowel is higher. Furthermore intraperitoneal therapy is contraindicated in the presence of adhesions, bulk disease and involved retroperitoneal lymph nodes (7).

A new approach that is still under research is the instillation of a radioisotope linked to a monoclonal antibody that is taken up by ovarian cancer cells. Early work with non-randomised patients has shown an improved survival for patients with no residual disease after surgery and chemotherapy compared to historical series. However, a randomised trial is needed and it is not clear how much the radioisotope influences response as the antibody itself could have anti-tumour activity (8).

GERM-CELL TUMOURS Germ-cell tumours are often extremely sensitive to radiotherapy, dysgerminomas more so than teratomas and, historically, cures were obtained with radiotherapy after surgery. However, whereas metastases from male germ cell tumours are largely confined to the lymph nodes, limiting the radiotherapy volume to the pelvis and para-aortic strip, in the female the peritoneum may be at risk if there is transgression of the ovarian capsule by tumour and therapy then has to be directed at the whole abdomen and pelvis.

Germ-cell tumours are also extremely sensitive to platinum-based chemotherapy and single agent platinum may be appropriate for early stage dysgerminoma whilst multi-agent chemotherapy is confined to those with more advanced disease or teratoma. Single agent cisplatin does not appear to prejudice fertility and even multi-agent chemotherapy may be followed by a successful pregnancy. This is in contrast to radiotherapy which inevitably causes sterility. Effectively, the advent of platinum-based chemotherapy has confined radiotherapy to a role in palliation for those few patients who cannot be cured by chemotherapy.

SEX-CORD STROMAL TUMOURS The commonest of these tumours is the granulosa cell tumour which is, nevertheless, extremely rare. There is no clear evidence that either radiotherapy

or chemotherapy enhance survival over that obtained by surgery alone. Tumours should be removed surgically even when recurrent and radiotherapy or chemotherapy reserved for unresectable disease, preferably as part of a clinical trial. Anecdotally, granulosa cell tumours are said to be of moderate radiosensitivity. However, progression of unirradiated disease may be extremely slow and radiotherapy should probably be reserved for masses that are symptomatic.

OTHER TUMOURS The ovary may be involved as a site of metastasis from tumours elsewhere, notably carcinoma of the stomach and of the breast. Treatment should be that dictated by the primary tumour and local radiotherapy to symptomatic masses may be palliative. Much more rarely the ovary may be involved by lymphoma, and treatment should be as dictated by the cell-type and distribution of disease, usually by chemotherapy.

Finally the ovary may be involved by a very rare primary tumour – sarcoma. Usually this is a malignant mixed Mullerian tumour although other sarcoma types may arise. There is no evidence that radiotherapy, or indeed chemotherapy, plays any part in extending survival and these tumours have a poor prognosis. Nevertheless adjuvant pelvic radiotherapy is often given following resection of early stage disease in the belief that this reduces the incidence of troublesome local recurrence.

CONCLUSION The role for radiotherapy as an adjuvant in the management of ovarian malignancies would appear to be a small one. There may be a small defined group of patients with minimal epithelial tumour burden either after surgery or after chemotherapy whose survival may be extended by whole abdominal radiotherapy or possibly by antibody-directed radiotherapy. However, the superiority of this over newly developing chemotherapy has to be proven. Although used as an adjuvant to surgery in sex-cord stromal tumours and sarcomas this role remains unproven and granulosa cell tumours should probably be managed surgically. Germ cell tumours should be managed by chemotherapy except for end-stage disease where radiotherapy has a proven role as a local treatment for palliation as it does for other tumour types.

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Radiation therapy in ovarian carcinoma

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INTRODUCTION In many western countries, ovarian cancer is the most common cause of death in women with gynecological malignant tumors. Epithelial ovarian cancer accounts for 90% of all malignant ovarian tumors, and only 30% to 40% of these are limited to the pelvis at initial diagnosis (1). More than two-thirds of patients present disease involving the abdomino-pelvic cavity and 25% of the patients are found to have upper abdominal involvement after appropriate staging procedures (2). Ovarian cancer disseminates over serosal surfaces and remains confined to the abdomino-pelvic cavity for most of its natural history. This dissemination pattern presents a major problem in the management of this malignancy with radiation, because treatment of the entire peritoneal cavity is required to encompass the tumor volume. For patients with early ovarian cancer, the 5-year survival rates are low, ranging from 50% to 75% for stage I disease and 25% to 55% for stage II disease. One important reason for the low cure rates in this subgroup of patients is that many patients have occult metastases in other areas of the abdomen, such as diaphragm, paraaortic nodes, the omentum, and other pelvic and abdominal peritoneal surfaces (1).

Optimal cytoreductive surgery when possible, followed by cisplatin based chemotherapy remains the primary treatment for most of the patients diagnosed with epithelial ovarian carcinoma. Although these combination regimens have produced high clinical response rates in patients with stage III and IV disease, pathological complete response rates as documented by negative second-look laparotomy are only 30-40%. Another 20-50% of patients with a negative second-look laparotomy will eventually recur (3). Advances in cytoreductive surgery and postoperative chemotherapy, in the last decade, reached a plateau. In such circumstances we are faced with the need to take other therapeutic decisions.

RADIATION THERAPY The use of radiation therapy in the management of ovarian cancer continues to be a controversial subject. Controversy arises from several factors, including the early use of inappropriate techniques and doses of radiation and the selection on inappropriate patients such therapy (4). To be of curative benefit in ovarian cancer, radiation therapy must encompass the sites in which disease is most likely to recur postoperatively. Techniques that encompass the whole peritoneal cavity, rather than just the pelvis or lower abdomen alone, are likely to be most beneficial. The dose of radiation that can be safely delivered to this large volume is low in comparision to that considered necessary to eradicate most solid tumors. Thus, it is expected that abdominopelvic radiation therapy would benefit only patients in whom the volume of residual tumor remaining postoperatively in the upper abdomen is microscopic (4). Several possible mechanisms may help explain the failure of radiation therapy to control bulky residual disease, the first one being the relatively low dose of radiation that can be safely delivered, due to the limited tolerance of the bowel, kidney and liver. The second mechanism is the possible development of cross-resistance to radiation of the chemotherapeutically treated residual tumor (5).

In selecting patients with early stages disease who are appropriate for abdominopelvic radiation therapy, the amount and site of residual disease and the tumor grade are strong determinants of successful outcome. The *„Dembo prognostic model"* for epithelial ovarian cancer took into account these prognostic factors and defined three groups: a low-risk group, an intermediate-risk group and a high-risk group. This classification of patients is currently used in Toronto to select patients for radiation therapy and to understand their outcome after treatment *(Table 1.)* (4). According the *Toronto data* (4), patients in the low-risk category receive no additional therapy. Those in the

Table 1. „Dembo prognostic model" for epithelial ovarian cancer. Adapted from *Thomas and Dembo* (4)

LOW RISK:	Stage I, RD=0,Gr 1
INTERMEDIATED RISK:	Stage I, RD=0, Gr 2,3
	Stage II, RD=0, Gr 1, 2, 3
	Stage II, RD<2 cm, Gr 1,2
	Stage III, RD=0 or <2 cm, Gr 1
HIGH RISK:	Stage II, RD<2 cm, Gr 3
	Stage III, RD=0 or <2 cm, Gr 2,3

(RD = Residual disease; Gr = Grade)

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intermediate-risk category, in whom abdominopelvic radiation therapy is most appropriate as the sole postoperative treatment method, showed a 10-year disease-free survival of 67%. On the other hand patients in the high-risk category, receiving the same radiation therapy, presented only 20% 10-year disease-free survival.

RADIATION TECHNIQUE Several techniques delivering radiation to the entire peritoneal cavity have been developed. The two most commonly used are the moving-strip technique and the open field technique. In the *moving-strip technique* a small part of the abdomen is sequentially irradiated every day. The duration of the entire treatment course is approximately twice that of the open field and, theoretically, the prolonged treatment course might allow accelerated proliferation of tumor and possible reappearance of tumor metastases from the untreated area of the peritoneum back to the previously treated area (4). In *the open field technique* the whole volume is treated every day. *Dembo et al.* (6) compared these two techniques and the 5-year survival rates were indistinguishable between the two treatment arms and the acute toxicity was also similar.

According to *Thomas and Dembo* (4) „an optimal therapeutic ratio might be achieved with abdominopelvic irradiation if the following technical principles were followed:
1. The entire peritoneal cavity is encompassed using an open field technique.
2. No liver shielding is used, thus ensuring an adequate dose to the right hemidiaphragm.
3. The upper abdominal dose should not exceed 22.5-28 Gy in 100-120 cGy daily fractions.
4. Renal damage is avoided by partial kidney shielding, limiting the renal dose to 18-20 Gy.
5. The true pelvis is boosted to a total dose of 45 Gy in 180-220 cGy fractions.
6. Parallel opposing portals are used, with each field treated daily to minimize the dose per fraction employed. The beam energy must be sufficient to ensure a dose variation of less than or equal to 5%."

EARLY OVARIAN CANCER The early stages of the disease, which account for approximately 30% of yearly reported cases, represent theoretically the subset of ovarian cancer patients with better prognosis. Overall, patients with stage I disease have an excellent long-term prognosis, usually more than 80% 5-year relapse-free rates. Stages IA or IB tumors with poorly differentiated histology, stage IC as well as stage II disease represent unfavorable prognostic categories associated with high-risk of relapse in the abdominal cavity (4, 7). Frequent recurrences in the peritoneal cavity have led to various postoperative therapies. Among the several techniques the most often used are chemotherapy, external beam radiation therapy to the whole abdomen, or intraperitoneal installation of a radiocolloid.

RADIATION THERAPY VERSUS OBSERVATION In the *Princess Margaret Hospital* study (9) patients with stage Ia disease were randomized to receive postoperative pelvic radiation therapy or observation. There was no benefit in survival or prevention of relapses for patients receiving pelvic radiation. Abdominopelvic radiation therapy has not been the subject of a phase III trial in patients with stage Ia disease, although some studies have included a few of these patients.

RADIATION THERAPY VERSUS CHEMOTHERAPY Various studies have been made in an attempt to compare the relative effectiveness of abdominopelvic radiation therapy versus combination platinum-based chemotherapy in intermediate-risk patients. The randomized clinical trails were unable to be complete, possibly as a result of strong investigator bias or the widely divergent treatment methods. Patient accrual was difficult and the studies were closed before completion (4).

Thomas and Dembo (4) concluded that there are no firm data on which to base a preference for either radiation therapy or platinum-based combination chemotherapy for intermediate-risk patients.

Chiara et al. (7) conducted in Italy a randomized clinical trial comparing cisplatin plus cyclophosphamide versus whole abdominal radiotherapy in high-risk early-stage ovarian cancer patients. The study was prematuraly closed because 63% of all patients in the series were treated with chemotherapy. The 5-year survival was 71% and 53%, while relapse-free survival was 74% and 50% for chemotherapy and whole abdominal radiotherapy respectively. The differences were not statistically significant, but a short-term chemotherapy, including cisplatin, appears to be a safe treatment in comparison whole abdominal radiotherapy.

The *M.D. Anderson Hospital* randomized trial (8) involved stage I, II and III patients. Abdomino-pelvic radiation was compared with 12 cycles of melphalan. All patients had neither gross residual disease nor disease < 2 cm in diameter. No survival difference was detected with 5-year survival rates, which were 71% in one arm and 72% in the other.

RADIATION THERAPY VERSUS CHEMOTHERAPY AND RADIATION THERAPY The *Princess Margaret Hospital* (9) conducted a randomized trial comparing abdomino-pelvic radiation to pelvic radiation plus chlorambucil. The trial involved patients with stages Ib, II or III asymptomatic. The results didn't show any significant overall difference with a 5-year survival rate of 60% in the abdominal radiation arm versus 43% in the chlorambucil arm. However, when the analysis was confined to those who had a hysterectomy and bilateral salpingo-oophorectomy, the difference was significant ($p<0.02$), with a 5-year survival rate of 78% in the abdominal radiation arm versus 51% in the chlorambucil arm.

In the *National Cancer Institute of Canada Clinical Trials Group* (10) patients, with stages I, IIA „high-risk" ovarian car-

cinoma and IIB, IIIO (disease confined to the pelvis), were randomized either to abdominal radiotherapy, to melphalan or to intraperitoneal chromic phosphate (^{32}P). All patients were initially treated with pelvic radiotherapy. No significant difference was observed between the three arms. The 5-year survival was 62% in the abdominal radiotherapy arm, 61% in the melphalan arm, and 66% in the chromic phosphate arm. Concerning the disease-free survival melphalan had a marginally significantly superior disease-free survival experience compared with abdominal radiotherapy (p=0.015)

The *Danish Ovarian Cancer Group* (11) performed a randomized study of early epithelial ovarian cancer (stages Ib, Ic and II), comparing the adjuvant effect of whole abdominal radiotherapy with pelvic irradiation plus cyclophosphamide. Overall survival did not significantly differ between the two regimens. 4-year survival for patients treated with whole abdomen radiotherapy was 63% and 55% for patients treated with pelvic radiotherapy and cyclophosphamide. Recurrence-free survival was also equal for the two treatments. In this study the irradiation volume was exactly the same as in the Toronto trial, so the lack of difference cannot be explained by a too small irradiation volume.

ADVANCED OVARIAN CANCER

RADIATION THERAPY FOLLOWING SURGERY AND CHEMOTHERAPY Despite combined treatment approaches, the survival rates in advanced stage ovarian cancer have shown little improvement in the last decade.

The benefit of radiation therapy as an adjuvant to chemotherapy in advanced stage ovarian cancer has not been clearly defined. *Arian-Schad et al.* (5) reported a retrospective study concerning 20 patients with FIGO stage III epithelial ovarian cancer who had undergone maximum cytoreductive surgery and a combination platinum-based chemotherapy and were treated with irradiation to the abdomen and pelvis followed by a pelvis boost. The 3-year overall survival is correlated with the amount of residual disease. It was 100% for patients with no residual disease, 66.7% for ≤ 2 cm, and 26.7% for those with > 2 cm residual disease. This approach appeared to be most effective in patients with no visible disease after initial surgery.

Calkins et al. (12), from the Johns Hopkins Hospital, showed the results of a phase II study, in patients with stage III disease, using a new technique – the delayed split abdominal irradiation or DSA. This technique was designed to accomplish two goals: first, to enable treatment of the entire peritoneal cavity and the pelvis on a single treatment day without undue acute morbidity and second, to deliver an adequate tumoricidal fractional dose of radiation, 1.5 Gy to the upper abdomen and 2 Gy to the pelvis. This was accomplished by dividing the abdomen into upper and lower halves treating the two fields separately with at least 6 hrs between fractions. The survival advantage from this study is difficult to determine in a non-randomized review, but the DSA irradiation is an acceptable technique for delivering a high fractional dose of radiation to the entire peritoneal cavity.

In a pilot study *King et al.* (13) assessed the feasibility of concomitant whole abdominal irradiation and intraperitoneal cisplatin chemotherapy in patients with advanced ovarian cancer. They concluded that this combination of radiotherapy and intraperitoneal chemotherapy confers no therapeutic advantage on patient with large residual disease and is more toxic than standard chemotherapy or radiation therapy regimens alone.

Other reported series have included patients with different surgical and chemotherapy treatments and varied criteria for evaluation of response. Moreover range of radiation techniques and dose have been employed. This lack of uniformity including the different sequences of therapeutic modalities applied contributes to the variations in treatment results. Prospective randomized trials comparing post-surgical use of chemotherapy alone with chemotherapy plus radiation are still lacking.

RADIATION THERAPY AFTER SECOND-LOOK LAPAROTOMY A second laparotomy is performed after completion of chemotherapy that usually requires 6 to 8 months. The merits of second-look laparotomies and further therapy are debatable. Some authors believe that the lack of acceptable treatment alternatives for patients with positive findings eliminates the need for this procedure. Second-look laparotomies in patients who are clinically free of disease are pathologically negative in 25% to 49% of cases (14). Recurrence rates after negative second-look laparotomies in ovarian cancer patients range from 5.9% to 50% (14). Therefore, it is believed that further consolidative therapy is needed in patients with negative second-look laparotomies.

Menczer et al. (15) from Israel, compared the outcome in two non-randomized groups of ovarian cancer patients in complete clinical remission who had minimal or no residual disease at second-look laparotomy. One group was treated after the reexploration with cisplatin intraperitoneal chemotherapy, the other one with abdominopelvic irradiation. The data of this study seem to suggest that the survival and the progression free interval duration of patients in complete clinical remission, who, subsequent to second-look laparotomy, were treated with intraperitoneal cisplatin chemotherapy are better than the ones of such patients treated by abdominopelvic irradiation. This difference was statistically significant only in patients with a negative second-look laparotomy.

In a *California phase II study* (16) the authors evaluated the role of whole-abdominal radiotherapy for patients with minimal residual tumor documented at laparotomy following initial surgery and adjunctive cisplatin-based chemotherapy. The results of this study were discouraging. Despite completion of the planned course of radiotherapy in 14 of the 16 treated patients, the overall median progression-free interval was only

9 months. Survival after documentation of progression was short.

The *Swiss Group for Clinical Cancer Research* (SAKK) decided in 1985 to study the feasibility and efficacy of whole abdominal irradiation after short-course chemotherapy (17). Their aims were to induce a high number of pathologically verified complete remissions with surgery plus 4 cycles of cisplatin and melphalan and to prevent relapse with whole abdominal irradiation in a target population of patients in remission. The study concluded that whole abdominal irradiation as a consolidation treatment can neither prevent relapse in patients with pathological or clinical complete response, nor be used as an efficient salvage treatment for patients with microscopic residual disease after melphalan and cisplatin. The whole abdominal irradiation was hardly feasible as a consolidation treatment for the majority of the patients in remission, even after a short-course chemotherapy.

Two randomized trials, published recently, try to clarify the role of the whole abdominal radiation after second-look in ovarian cancer patients responding to surgery and chemotherapy. The Italian group (18) presents the results of a randomized study in which advanced ovarian cancer patients with pathologically confirmed complete response or with minimal residual disease after second-look (<2 cm) were treated with whole abdominopelvic radiotherapy or with three additional courses of the same chemotherapy that induce the response. With a median follow-up of 22 months the analysis of the results shows: the disease progression was observed in 11 of 20 patients (55%) treated with radiotherapy and in 6 of 21 patients (28.5%) treated with chemotherapy (p=0.08); the disease-related deaths occurred in 9 patients in the radiotherapy arm (45%) and in 3 patients (14.2%) in the chemotherapy arm (p=0.02). In conclusion the chemotherapy was more effective than radiotherapy in controlling disease progression after surgery and front-line chemotherapy in patients with no or minimal residual disease at second-look.

The second trial comes from the *North Thames Ovary Group Study* (19) with the aim of determining, in a randomized trial of advanced ovarian carcinoma, whether consolidation therapy with whole abdominal radiotherapy after chemotherapy improves survival and disease-free survival compared with the same continued chemotherapy (5 courses of carboplatin). All patients received, before response evaluation, and after initial surgery, five monthly courses of carboplatin. The data reported don't show any significant difference between both groups, concerning overall survival or progression-free survival. There was also no difference in survival among patients in whom no residual disease was found at second-look.

SALVAGE RADIATION THERAPY Patients with advanced and recurrent ovarian carcinoma continue to pose a therapeutic challenge and demonstrate a need for evaluating alternative treatment modalities to improve on the existing low survival rates.

To evaluate the role of whole abdomen radiation therapy with a pelvic boost as a salvage therapeutic modality, *Reddy et al.* (3) treated patients with ovarian carcinoma who had failed initial systemic chemotherapy. The 4-year actuarial survival and recurrence-free survival rates for the entire group of 44 patients were 23% and 22% respectively. The survival and the recurrence-free survival rates for the group with microscopic residual disease at 37% and 42% were significantly better than those for patients with macroscopic residual disease at 9% and 5%, respectively. The whole abdomen radiation therapy with a pelvic boost is feasible as a salvage therapeutic modality with minimal acute and late toxicity. The data suggest that this method of treatment is effective in management of patients with minimal residual disease (20).

In another study from the *Fox Chase Cancer Center,* in Pennsylvania (21), 33 patients with recurrent ovarian cancer were irradiated to 47 sites (pelvis, abdomen, chest, brain, etc.). Abdominopelvic fields were not designed to cover the whole abdomen but were tailored to include the gross tumor volume with additional margin to irradiate the planning target volume adequately. For the entire group, the complete symptomatic response was 51%, and the overall symptomatic response was 70%. This is the first published analysis to evaluate the palliative efficacy of radiotherapy rigorously among a group of patients whose initial care included agressive debulking surgery and cisplatin based chemotherapy. The analysis concluded that durable palliation can be achieved with radiotherapy in most patients with recurrent ovarian cancer.

RADIATION THERAPY TOXICITY

ACUTE TOXICITY According to the *Princess Margaret Hospital* (9) study the acute toxicity was similar in both techniques of whole abdomen irradiation – moving-strip and open field. Fatigue, which increases as treatment progresses, is the most common complaint. Anorexia, meteorism, mild diarrhea and nauseas are very common. Vomiting is occasional and, in general, hematologic toxicity is mild (4). Treatment interruption for acute toxic effects is rare, if radiation therapy is the sole post-operative therapy. Acute symptoms tend to disappear within a few weeks of treatment completion.

LATE TOXICITY Pneumonitis or lung fibrosis and gastrointestinal damage, consisting of bloating or intermittent diarrhea related to particular foods, occur in 5-20% of patients (4). Approxi-

Table 2. Summary of late bowel complications after abdominopelvic irradiation

Serious complication rates:	
Low dose (2250 rad/22 fractions)	1.4%
High dose (3000 rad/8 fractions)	14.3%
Bowel surgery	5.6%
Deaths	0.4%

(adapted from Thomas and Dembo (4)

mately 50% of patients have elevated alkaline phosphatase levels transiently, but clinical evidence of liver damage is rare (4). *Table 2.* adapted from *Thomas and Dembo* (4), summarizes the major bowel complications from 1098 patients in 10 series.

The frequency of serious gastrointestinal morbidity and its severity appears to be related to the total dose of radiation, the dose per fraction, and the extend of previous surgery, particularly lymph node sampling (4).

RADIOACTIVE ISOTOPES Colloids labelled with radioactive isotopes of phosphorus or gold have been used. ^{32}P is the most attractive isotope, given that is a pure beta emitter. Despite the intuitive appeal of the use of intraperitoneal ^{32}P, a therapeutic value has not been established for this therapy.

Epenetos at al. (22, 23) since 1983 have been investigating the possibility of tumor targeting and therapy by the intraperitoneal administration of radiolabelled monoclonal antibodies in patients with ovarian cancer. They treated a group of 52 ovarian cancer patients with yttrium-90-labelled monoclonal antibody HMFG1 administered intraperitoneally following conventional surgery and chemotherapy. The treatment was well tolerated and this study suggests that patients with advanced ovarian cancer who achieve a complete remission following conventional therapy may benefit from further treatment with intraperitoneal radioactive monoclonal antibody.

INTRAPERITONEAL ^{32}P IN EARLY STAGE As it was said before the *NCI Canada* trial (10), comparing adjuvant treatment with abdominal radiotherapy, melphalan or intraperitoneal ^{32}P did not show any difference concerning survival between the three arms.

A randomized trial comparing cisplatin (50 mg/m2 – six courses) with intraperitoneal ^{32}P or whole abdomen irradiation as adjuvant treatment of ovarian cancer patients (FIGO stages I to III disease without residual disease after laparotomy) was accomplished by the *Norwegian Radium Hospital* (1). Patients randomized to received ^{32}P with extensive intraperitoneal adhesions were treated with whole abdominal irradiation instead of ^{32}P. Crude and disease-free survival were similar in both groups. Late bowel complications occurred more often in patients treated with ^{32}P compared with the cisplatin group. Because of this high number of late bowel complications after ^{32}P the authors recommended that cisplatin must be used as standard adjuvant treatment for subsquent controlled studies.

Considering the short penetrating power of ^{32}P, the dose to the retroperitoneal nodes is negligible, and the radiation dose distribution over the peritoneum is often variable and unpredictable. *Soper et al.* (24) treated 49 women with apparent stage I and II ovarian cancer with intraperitoneal ^{32}P and confirm that their experience shows the failure of adjuvant ^{32}P as adjuvant therapy to prevent extraperitoneal recurrences in women with apparent early-stage ovarian carcinoma who have undergone only casual surgical staging procedures. For this reason ^{32}P is not appropriate therapy for this kind of patients.

INTRAPERITONEAL ^{32}P AT SECOND-LOOK LAPAROTOMY In the *Norwegian Radium Hospital study* (25) 50 patients with negative second-look findings were assigned randomly to receive intraperitoneal ^{32}P or no treatment and the results of the log-rank test for differences in survival distributions between the two groups were not significant or even suggestive of a prolonged survival in the ^{32}P arm.

Two other non-randomized studies (14, 26) treating patients without evidence of disease at second-look laparotomy with ^{32}P concluded that postsecond-look intraperitoneal ^{32}P treatment improved the progression-free survival and possibly overall survival rates.

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Technical considerations and complications of radiation therapy of gynecologic malignancies

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ABSTRACT The design of radiation fields and the modality of radiotherapy for gynecologic malignancies must aim at decreasing treatment-related toxicity. Many patients develop acute and chronic complications of varying severity, particularly regarding the genitourinary and gastrointestinal tissues. We will discuss some simple radiotherapeutic techniques to carry out to minimize radiation injury and to optimise the treatment.

Key words Pelvic radiotherapy, radiotherapic techniques, complication.

INTRODUCTION At the present time the two main modalities of irradiation for gynecologic cancers are either external photon beam or brachytherapy. The anatomic structures of the pelvic relevant to the planning of the radiation therapy can be diveded in two groups. The first one, which includes the vagina, uterus, paracervical and paracolpal areas and medial parts of the uterine ligaments (central disease) is often primarily irradiated with intracavitary sources. These structure have a changeable relationship to the pelvic bone and other surrounding organs, depending on the age of the patient, locoregional extension of the tumour, previous surgical treatment and so forth. The second group, which includes the lateral aspects of the uterine ligaments and the pelvic lumph nodes, has a fixed relationship to the pelvic bone. Adequate external radiation therapy requires to cover a large target volume. Fields include laterally pelvic brim at least 2 cm margins; the superior edge is at the top of the sacrum or 4-5 cm above highest positive lymph nodes. The location of the lower margin is critical: the location or the uterine cervix or vagina tumour extension can be determined by using some cervical markers. In any case, the design and delivery of radiation therapy for gynecologic cancer require a particular care to minimize the dose to the normal organs encompassed in the irradiated volume (small bowel, rectal mucosa, bladder) and to preserve the reproductive function in children and fertile patients. The use of proper equipment, implementation of methods to decrease treatment-related toxicity and a close collaboration with the physics are essential: every attempt must be addressed to reduce the irradiated volume to a minimum, to avoid normal tissues whenever possible or to keep the dose to them as low as possible to prevent radiation injury.

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Complications of pelvic radiation therapy are a function of the volume of the radiation field, distribution of the dose within the treated volume, overall treatment time, fraction size, radiation energy, total dose and technique (1). Furthermore, a variety of individual factors modifies individual tolerance. In fact, the radiation response of pelvic structures depends to a lesser degree on other factors including age, other medical problems (e.g. obesity, diabetes, vascular disease, abnormal level of haemoglobin, leukocytosis), race and socio-economic level of the patient, previous treatment (surgery, irradiation or chemotherapy) or pelvic inflammatory disease (2). The technique must be at acceptable limits of normal tissue pelvic tolerance and every increase of morbidity must correspond to improvement of overall survival (3). Anyway, a certain percentage of radiation-induced complications is unavoidable. With advanced disease higher risks of injury are considered, because these cases require not only larger portals but also higher doses and, furthermore, have often already compromised the integrity of the bladder and bowel. The optimum dose to the primary lesion is often established considering the radiation tolerance of the rectum, rectosigmoid, bladder and small bowel.

TECHNICAL CONSIDERATIONS The susceptibility of the large bowel to radiation injury is a major factor in determining which of the many technique is preferable. The volume of small bowel in pelvic fields can be reduced through customized field shaping and through displacement of the small bowel out of the pelvis. This displacement can be obtained in different way : using immobilization mold, which consists of a device with a hole superior to the level of the radiation field

where set the small bowel, having the patient maintain a full bladder or placing the patient in a prone position, so that the gravity and pressure displace the small bowel anterior and cephaled. There is a significant decrease in the average small bowel volume when the patient are treated in the prone position with the combination of abdominal wall compression and bladder distension, compared with the supine position. There are also surgical techniques to keep the small bowel out of the pelvis and to minimize injury, such as the use of an absorbable synthetic Vicryl, which temporarly removes the small bowel from the pelvis and is completely reabsorbed within 3-5 months. The use of clips in the high-risk areas at time of surgery helps to better define the target volume. The normal motility of the small bowel usually prevents the administration of excessive doses to any one segment. However, previous pelvic surgery, pelvic inflammatory disease or the extension of cancer to the peritoneal surface reduce significantly pelvic tolerance and increase the frequency of adhesions. In such instances the incidence of small bowel radiation injures increases sharply and pelvic radiotherapy is more difficult. The use of a four-field technique further decreases the volume of small bowel treated and a carefully fractionated irradiation of the smallest possible volume assures a minimum of such complications, but the risk must otherwise be accepted.

Some simple radiotherapeutic techniques are available to decrease radiation-related toxicity (4). With regard to the energy, because of the thickness of the pelvis high-energy photon beams are suited. Optimal pelvic external irradiation can be provided with 6 MeV or higher energy x-rays as produced by a linear accelerator, which, by nature of its depth dose characteristics, delivers a higher dose to the target volume while sparing the surrounding normal tissues (particularly rectum and bladder) and provides a more homogeneous dose distribution within the pelvis. With regard to the technique, patients can be treated using an isocentric rotation, four-field box or three-field isocentric treatment, depending on the size of the patient and the equipment available (5). More frequently, employing a linear accelerator of low energy (4-10 MeV) a four-fields arrangement is chosen, so that the resulting uniform high dose area resembles the shape of a brick or a box. A pair of parallel opposed anterior and posterior fields and parallel opposed left and right lateral fields are used. The anterior and posterior fields include the entire bladder and the rectum, while only the posterior portion of the bladder and the anterior segment of the rectum and much of the sigmoid colon are included in the lateral fields. The weighting of these fields may be manipulated until the optimum dose distribution is achieved. If needed, the use of wedges on the lateral fields can decrease the total dose to the femoral heads. The use of multiple-field techniques (3 or 4 fields) allows a larger amount of small bowel to be blocked from the pelvis compared with an AP/PA (2 fields) technique. High energy linear accelerator with more penetrating beams of 18-25 MeV or greater could allow simpler treatment plans with parallel opposed AP/PA fields only. Whichever technique is used, all portals should be treated daily, so to give a lower biologically effective dose to those structures in only some of the fields. Ideally, all fields are treated with the patient in the same position through an isocentric technique. Particular attention must be paid during the treatment simulation. Simulation film should be taken with radiopaque markers. A clip or a vaginal cylinder covered with barium should be placed in the vagina and a catheter in the rectum for insertion of barium to localize these structures on the lateral film. Also the bladder can be visualized with air or gas in the lumen. Small bowel contrast is essential to determine its position, so the fields can be blocked or shaped to minimize exposure of this part. Computed tomography image of the pelvis, with the patient in treatment position, facilities treament planning and optimize dose distribution within the target volume.

The pelvic structures to be included in the treatment volume differ according to the site and stage of the disease. In the case of uterine cervix and endometrial carcinoma, the fields should extend superiorly to the top of the fifth lumbar vertebra for including the common iliac node (if common iliac node coverage is not indicated, the suprior field margin is reduced to L 5-S1 interspace), inferiorly to the midobturator foramen or down to the introitus if the vaginal wall is invaded, laterally to encompass the pelvic brim with a minimum 1.5 cm margin lateral to the widest diameter of the pelvic outlet. Contrast remaining in the nodes from lymphangiography or clips placed in the region of the nodes at the time of limphadenectomy are very useful in determining this margin. The lateral fields should cover the iliac nodes anteriorly and the sacral nodes posteriorly, but sparing unnecessary irradiation of bone and the posterior half of the rectum. Metastases in common iliac and paraaortic lymph nodes involved that longer segments of small bowel must be irradiated, because fields extend up to the level of the dome of the diaphragm. The use of lateral portals for some of the dose decreases small bowel damage (6-7). The treatment of primary carcinoma of the vagina usually involves a target volume similar to that employed for cancer of the cervix, but longer lenghts of vagina are included. For distal lesions, the inguinal lymph nodes may be treated as well. In the case of ovarian carcinoma, since it may spread throughout the abdomen, radiotherapic portals generally employ treatment of the entire abdomen with a boost to the pelvic and/or periaortic volumes. In patients where it is necessary to treat the whole pelvis and the entire length of the periaortic nodes, it is preferable to treat the entire volume without introducing the moving strip technique to avoid possible under and overdosage at the junction between several fields.

The dosage is a very important complication related-factor. The fractions dose may range from 150 to 200 cGy per day with 5 fractions given per week. Fractions of 150 to 170 cGy minimize acute normal tissue reactions and decrease the need for interrupting treatment. Fractions of 250 cGy have been tried for split-course irradiation, up to 10 fractions followed by a 2-week rest, and then 250 cGy in 10 fractions of pelvic irradiation, with both courses followed by intracavitary brachy-

therapy, but the concept of split-course irradiation is not recommended for routine use. Multiple daily fraction schedule, used for palliative aim, demonstrates a higher potential late complication rate in long-term survival patients (8).

When intracavitary brachytherapy is to be used, the dose to the whole pelvis from external irradiation varies from 4000 to 5000 cGy calculated at the midpelvis. Dose variations in the irradiated volume should not exceed 10%. One or both parametria or pelvic walls may be boosted to a higher dose (500 to 1000 cGy) for bulky tumours or residual involvments. The midline normal structures should be shielded with an appropriated lead block during a boost dose of external irradiation or during part of the whole pelvis irradiation. Brachytherapy may be the sole treatment modality for initial cancer of the cervix or for cancer of the endometrium in medically inoperable patients. Traditional brachytherapy system has been low dose-rate (LDR), with typical implant of 24-72 duration. The most important reason for using LDR is the large experience that has been gathered from the last decades, but, in addition, minimisation of side effects and late complications in organ at risk. LDR technique is also less labour intensive than high dose-rate (HDR) because of only one or two fractions being used. For most of the LDR regimes there exist effort to establish equivalent regimes in terms of time-dose-fractionation (9). In clinical practice the number of HDR fractions range from four to seven, but the optimal schedule has not been yet found. A very important feature of HDR technique is the excellent geometrical precision, due to the short treatment times. In addition, there is with HDR technique the possibility of effective optimisation of the dose distribution; individualized treatment planning is essential as is accurate reconstruction of source dwell positions with regard to applicators, target volume and radiation sensitive organs. A very promising method to combine the better therapeutic ratio of LDR and the possibility of optimisation is the use of pulsed low dose-rate (PDR) tecniques. In PDR, a single source of medium strength activity simulates a LDR treatment by means of multiple pulses of short duration (10). Until now this technique in not in routine clinical use.

Innovative techniques using 3-D treatment planning consent to plan and localize the target and normal tissues better than using only a single central transverse slice or simulation films. This technique has been applied to intracavitary gynecologic implant employing a CT-compatible applicator and a CT-based treatment planning system with 3D capability (11). It demonstrated the delivery of much higher bladder and rectal doses than predicted by conventional dosimetry methods and the delivery of lower doses to the cervix than classically estimated by point A dose.

EARLY AND LATE COMPLICATIONS IN PATIENTS RECEIVING PELVIC IRRADIATION Most of the patients treated with radiotherapy for gynecologic malignancies will develop some degree of acute and chronic pelvic reaction of varying severity. Two groups of complications are recognised, the acute early and the chronic late reaction (12).

EARLY COMPLICATIONS The most consistent, acute radiation reaction is a change of bowel habit due to the combined impact of treatment on small bowel, sigmoid, and rectum because these are more susceptible to radiation injury then other pelvic organs. This normally causes increased bowel movements with diarrhoea, tenesmus and some colic approximately two weeks after starting therapy. If irradiation has been particularly vigorous, the diarrhoea that develops may be bloody (13). The daily dose has a considerable influence; with 150 cGy daily fractions, these acute reactions are less frequent than with the usual 180 to 200 cGy dose (14). The diarrhoea may be controlled with paregoric or diphenoxylate, bed rest, and a low-residue diet. Rarely other measures will be necessary. However in some patients the severity of the acute reaction is such that even when it settles it precludes further external-beam radiotherapy and an alternative surgical or intracavitary approach may be required (15). Another important acute reaction concern the urinary bladder, where may appear dysuria and frequency at approximately the same time as the bowel reaction. Proof of his radiation induced pathogenesis is the sterility of the urinary culture and the only way to treat it is the use of symptomatic measures including analgesics and antispasmodics.

All acute radiation reactions are normally resolved by 6-8 weeks (16). The majority of patients settle after their acute reactions and remain well for a minimum of 6 month (17).

LATE COMPLICATIONS In spite of a variety of individual factors modifies individual tolerance we can consider the following assertions as baseline from which one may extrapolate. When external pelvic irradiation is used as the single treatment for advanced cancer of the cervix, 7000 cGy to the midpelvis in 7 to 8 weeks is close to the limit of tolerance. When brachytherapy is used and a dose of 6500 cGy divided in two increments in 2 weeks is delivered to point A, an additional parametrial dose of 4000 to 5000 cGy given by external irradiation with a central block for one half of the dose is near the maximum tolerated. Finally, an initial whole-pelvis dose of 4000 cGy given by external pelvic irradiation without a midline shield should generally be supplemented by no more than 5000 cGy from intracavitary brachytherapy (15). With the more advanced clinical stages of disease, higher doses from external irradiation are necessary and grater risks of bowel damage are justified in fact most of the bowel wall thickening bowel obstruction, and fistulas develop in patients who have large central cancers or stage III or stage IV lesion. From 2 to 4 month after starting treatment, premenopausal women will develop menopausal symptoms of variable severity if their ovaries were included in any radiotherapy field. A positive decision needs to be made about whether to institute hormone replacement therapy (18). Late tissues changes in the surrounding pelvic tissues are

inevitable after radical radiotherapy but their range, severity, and time of onset are very variable (19).

International grading system commonly group genitourinary and gastrointestinal complication into four or five categories. For the Europe groups the most useful is the system reported in the "French-Italian Glossary" that describes five degree of increasing severity (0 to 4) in 14 organs and/or normal tissues:
G0: Absence of complications or acute reversible symptoms or signs which do not modify the planned course of treatment.
G1: Mild complications. These complications are mildly disabling and may cause some functional impairment.
G2: Moderate complications. Both obvious symptoms and sign are present resulting in intermittent or persistent interference with normal activity.
G3: Severe complications. Any acute or chronic symptoms or signs which are life-threatening either per se or because of the treatment required. Any permanent and severe tissue and/or organ damage.
G4: Documented evidence that death is due to the primary treatment, or to the complications of treatment, or to the treatment of complication(s) (20).

In summary, any death which is considered (even partially) as a consequence of a complication of treatment of cancer.

The radiation damage is a consequence of stromal and vascular change that produces thinning or ulceration, neovascularization, and/or fibrosis. These reactions manifest themselves as spontaneous bleeding, disordered function, ulceration, perforation and even fistula formation. Gastrointestinal symptoms may appear from 6 month to 10 year after treatment and are those of sever bowel irritation, that is, painless, fresh, rectal bleeding with or without a change of bowel habit and occasionally a burning sensation in the rectum. Local late rectal ulceration generally heals with conservative management. A good stool softener and paregoric or diphenoxylate to decrease bowel motility promotes healing in the majority of patients. Occasionally, steroid enemas may be required. The complications of perforation either into the vagina or into abdominal organs or obstructions are unusual and are considered surgical problems. The bowel superior to the rectum may also develop signs of radiation damage from intracavitary brachytherapy. This is particularly likely when a loop of the sigmoid colon falls into the cul-de-sac or remains relatively fixed in the high dose treatment volume. Symptoms consist of those of partial low bowel obstruction, bright blood and mucus in the stool, and alternate diarrhoea and constipation. Barium enema reveals a narrowed segment with rigid walls. This may progress to complete obstruction requiring surgical relief. Severe radiation proctitis or sigmoiditis may require a temporary colostomy for its management (19). The less frequent large bowel reaction from high dose external pelvic irradiation appears as a woody induration completely encompassing a segment of the rectum or rectosigmoid and presents symptoms similar to that described before. Almost from the beginning there is a narrowing of the bowel lumen that may become so severe that colostomy is necessary. The cause of this type of reaction has never been definitely established, although bowel epithelium, submucosa, small and large blood vessels, and surrounding connective tissues all show radiation-induced changes (21).

Genitourinary complications more commonly appear between 1 and 4 years. These are mainly cystitis, bladder ulcer, ureteral stricture, incontinence, urethral stricture or extensive cystocele. Urinary bladder complications are more frequent than ureteral complications and consist of two main syndromes:
1) painless haematuria due to posterior bladder wall telangectasia;
2) mild, chronic frequency due to reduced bladder capacity (12).

Radiation damages to the ureter can cause obstruct the organ resulting from radiation-induced periureteral fibrosis. The dose delivered to the ureter and to the parametrium is of course highly important in the causation of ureteral stricture, yet the stricture seems to occur at the lower dose levels as well as at higher level. However with conventional intracavitary brachytherapy techniques and their modifications, late ureteral obstruction is indicative of disease recurrence in the parametrium until proved otherwise. If recurrent cancer is not found, the stricture should receive the same treatment as in any other non cancerous patient.

In attempt to make a relationship between early and late complication we have to consider some important concept:
- the difficulty of define what constitutes an early complication, since such a clinical definition is susceptible to a number of semantic and patient-observer variables.
- because of the long latency that may exist between complication, since such a clinical definition is radiation therapy and the development of a late complication, patient may die of desease-related or intercurrent illnesses before a given late complication as time to manifest itself.
- any given late complication may or may not become symptomatic depending on hitherto unknown patient-related biological and physical factors (15).

For these reasons the relationship between early and late complication is not clear and even because few studies have been undertaken to determine that. However radiation oncologists are aware that the incidence and severity of late complications tend to increase as the acute radiation reaction becomes more severe. It should be pointed out that an early reaction also if vigorous is not necessary followed by a late reaction as well as the absence of an early reaction does not ensure that a late complication will not occur (22).

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Technical consideration and complications of surgery plus radiotherapy versus surgery alone in cervical cancer (Results from Italian study and a proposal for a new classification)

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Department of Obstetrics and Gynecology Institute University of Torino,[2] Padova,[4] Milano-Monza,[5] Genova,[7] Brescia,[8] Varese[4] and Department of Radiotherapy-Pinna Pintor Clinic[1]

ABSTRACT The aim of this study is to evaluate the complications observed in two groups of patients affected by cervical cancer, one treated with radical surgery and the other with radical surgery followed by radiotherapy when adverse prognostic factors were present.The complications were classified according to the glossary defined in advance and accepted by the 19 Italian Institutions which partecipated in the study.

In this paper we presented some preliminary results regarding cervical cancer treatment complications in stage T1b-T2a patients using the glossary proposed. The majority of the complications were urinary, followed by gastrointestinal, pelvic and genital. It is also important to stress that the majority of complications were mild or moderate (G1 or G2) and functional. The fact that we found a lot of mild (G1) and moderate (G2) complications suggests that these events migth be evolutive and could worsen if the treatment and the follow-up were not correct.

Key words Cervical cancer, therapy, complications.

Analysis of complications in the treatment of cervical cancer should be carefully considered together with survival, in evaluation of results of therapy (1, 2). Complications are not always looked at and systematically recorded during follow-up, and papers in which this factor is discussed make use of varying criteria and often evaluation is subjective (3-6). Moreover, it is difficult to compare different studies since the characteristic and the periods of observation of the population studied, are different and can not be standardized. Furthermore, the type of complication itself is influenced by the strategy employed: surgical may become apparent early, whereas radiotherapeutic damage may appear later. Even authorities on complicatios differ markedly in their evaluations (3-6). Some papers list solely subjective disturbances, others confine themselves to certain types of complications (e.g. early or late complications, fistulae or stenosis). Many other authors confine themselves to complications induced by the treatment they use, and compare these with the complications observed by others using the same strategy; no comparison is made with complications caused by alternative treatments (3-6). A further difficulty is the lack of a common terminology to classify the complications independently of the treatment employed (3-6). To overcome these difficulties, we set up a glossary in order to classify the complications induced by treatments of gynecological malignancies (4-5). This glossary has been compiled independently of the treatment and applied in different clinical situations to evaluate its compliance and effectiveness.

The aim of this paper is to evaluate the complications observed in two groups of patients affected by cervical cancer, one treated with radical surgery and the other with radical surgery followed by radiotherapy if negative prognostic factors were present. The complications were classified according to the glossary defined in advance and accepted by the different Institutions which participated in the study.

MATERIAL AND METHODS In 1982, a National study was begun in Italy in order to evaluate the complications arising in the treatment of cervical cancer. The study was developed as follows:

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1. A glossary of complications was compiled by the Institution coordinating the study.
2. A retrospective pilot study was made to verify the applicability of the glossary in different institutions.
3. Because the pilot study was positive, a prospecive cooperative study was started and 19 Italian institutions become involved.

Since the aim of the study was to classify complications independently of treatment, each institution was asked to declare the protocol in use and to accept the common glossary in reporting complications.

Table 1. Description of degree of complication (For a complete glossary reporting complications in gynecological cancer see ref. 5)

DEGREE OF COMPLICATIONS	
DEGREE 0 (GO)	Inevitable sequelae or side effects which are intrinsic to the treatment
DEGREE 1 (G1)	mild complications, moderately disabling and possibly causing some functional impairment, ranging from plain side effects (like episodic diar rhoea during radiotherapy) to situation perhaps requiring surgery (as hydronephrosis)
DEGREE 2 (G2)	Moderate complications with both signs and symptoms evident; complete healing often no achieved, but stabilization and amelioration obtainable with prolonged treatment. Ranging from moderate rectal bleeding to fistulae.
DEGREE 3 (G3)	Severe complications are more consistent, possibly with severe disabling disorders and/or permanent damage to tissue or organs; complications with obvious clinical signs
DEGREE 4 (G4)	Lethal complications, with death the result of treatment of the primary disease, of the complications or the treatment of complications

From January 1st 1983 to June 30th 1987, 2757 patients with histologically demonstrated cervical cancer, were registered in the study. All the patients were staged according to FIGO rules and the distribution by stages was as follows: Tis 569; T1a 164; T1b 1041; T2a 308; T2b 384; T3 237; T4 54. The patients were treated and followed by the participating institutions. Information regarding the course of the disease (recurrences or death) and the complications observed was recorded on standard forms in wich the complications were reported both as a description of the event (e.g. vesico-vaginal fistula) and as codified using the glossary. Data were analysed after the last patient involved was followed up for a least 5 years or had died. Because complications can evolve, they were classified as the worst degree of clinical evolution. Following the glossary, the complications were referred by organ and system and ranked in four degrees of severity (G1-G4). Patients with multiple complications were taken into account and different complications in the same patient were recorded separately. *(Table 1)*

RESULTS Within the 2757 patients in the study, 1349 were classified as stage T1b-T2a. Of these 295 (group A) were treated by radical hysterectomy (Piver III) with lymphadenectomy, and 280 (group B) received external radiotherapy after surgery (Piver III) due to poor prognostic factors such as tumour-size over 40 mm in diameter, cut-through surgery, positive lymph nodes, deep stromal involvment, higher grade of differentiation and capillary-like space invasion. The analysis of complications was done in these two group of patients. The 5-year survival was 86.7% in group A and 7% in the group B. Within these two groups, we observed 141 patients with complications in group A and 137 in group B. The total complications observed were 243 (some patients had more than one complication) in each group. The median onset time was 1 month (range 0-81) in group A, 4 months (range 0-81) in group B. *Table 2.* shows the distribution of the patients with multiple complications by treatment.

Table 2. Distribution of patients with multiple complications by treatment

Number of complications for patients	Group A	%	Group B	%
1 complication	74	52.5	71	51.8
2 complications	41	29.1	36	26.3
3 complications	17	12	20	14.6
4 complications	9	0	10	7.3
TOTAL	141	6.4	137	100

The distribuition of complications by degree of severity and the systems involved in the two groups is reported in *Tables 3.* and *4.*

Table 3. Distribuition of complications by degree of severity and system in group B.

Systems	1Gr.	%	2Gr.	%	3Gr.	%	4Gr.	%
gastrointestinal	27	22.5	6	6.3	2	9.1	0	0
urinary	55	45.8	69	71.8	8	36.4	0	0
vascular	9	7.5	9	9.3	3	13.6	5	100
cutaneus	13	10.8	0	0	5	22.7	0	0
genital and pelvis	3	2.5	2	2.1	1	4.5	0	0
bone	1	0.8	0	0	0	0	0	0
neurolog	2	1.7	2	2.1	1	4.5	0	0
hemopoietic	9	7.5	6	6.3	2	9.1	0	0
other	1	0.8	2	2.1	0	0	0	0
TOTAL	120	100	96	100	22	100	5	100

Table 4. Distribution of complications by degree of severity and system in group B

Systems	1 Gr.	%	2 Gr.	%	3 Gr.	%	4 Gr.
gastrointestinal	24	17.1	6	7.9	8	29.6	0
urinary	41	29.3	40	52.6	12	44.4	0
vascular	20	14.3	13	17.1	0	0	0
cutaneus	12	8.6	0	0	3	11.1	0
genital and pelvis	30	21.4	7	9.3	2	7.4	0
bone	0	0	1	1.3	1	3.7	0
neurolog	7	5.0	1	1.3	0	0	0
hemopoiet	6	4.3	5	6.6	1	3.7	0
other	0	0	3	3.9	0	0	0
TOTAL	140	100	76	100	27	100	0

Table 5. shows the distribuition of complications in the different organs and systems by treatment. In group A urinary complications were more widespread, above all those related to the bladder: 113/132 (85.6%). Of these 113 complications of the bladder, 104 were functional, 41 G1 and 63 G2. Also within group B, the most important complications were urinary, distributed as far as the severity and organ is concerned, in the same way as group A. However, we observed an increase in pelvic and genital complications (group A 6/243; group B 39/243 P= 0.005). We did not find any difference in the complications observed regarding gastrointestinal, vascular and cutaneous complications. *Table 6.* shows the distribution of complications by system and organs in both groups.

Table 5. Distribuition of complications by system and organ (Total N° of complications group A/B= 243)

Systems	Group A	%	Group B	%
gastrointestinal	35	14.4	38	15.6
urinary	132	54.3	93	38.3
vascular	26	10.7	33	13.6
cutaneus	18	7.4	15	6.2
genital and pelvis	6	2.5	39	16.1
bone	1	0.4	2	0.8
neurolog	5	2.1	8	3.3
hemopoiet	17	7.0	12	4.9
other	3	1.2	3	1.2
TOTAL	243	100	243	100

Table 6. Distribution of complications by system and organ (total N° of complications group A/B=243)

System	Organ	Group A	%	Group B	%
Gastroint.	Rectum	33	13.6	20	8.2
	Sigmoid	0	0	3	1.2
	Small Bowel	2	0.8	15	6.2
Urinary	Bladder	113	46.5	73	30.1
	Ureter	19	7.8	20	8.2

CONCLUSIONS Here we presented some preliminary results in abbreviated form regarding cervical cancer treatment complications in stage T1b-T2a patients using the glossary proposed by our institution and adopted by other participating centers. The glossary enabled us to classify and report the complications observed in the two groups of patients. As previously stated, the majority of the complications were urinary followed by gastro-intestinal, pelvic and genital. It is also important to stress that the majority of the complications were mild or moderate (G1 or G2) and functional. The fact that we found a lot of mild (G1) and moderate (G2) complications suggests that these events might be evolutive and could worsen if the treatment and the follow-up were not correct.

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Címoldal. A címoldal tartalmazza a közlemény címét, alatta a szerzők teljes nevét, a szerzők munkahelyét, (az osztály vagy intézet vezetőjének nevét nem kell külön megadni), egy rövidített címet, amely ne legyen hosszabb, mint 50 karakter, és a levelező szerző postacímét, telefonszámát.

A második oldal egy magyar nyelvű összefoglalót és 3-4 kulcsszót tartalmazzon. A kulcsszavak csak az Index Medicus Medical Subject Headings szavai lehetnek. A harmadik oldalon az összefoglalónak és a kulcsszavaknak angol nyelvű változatát kell megadni. Az angol nyelvű összefoglalóban szerepeljen a dolgozat angol címe és a szerzők neve is.

Szöveg. Az *eredeti közleményeket* hagyományos módon: bevezetés, anyag és módszer (vagy betegek és vizsgáló módszerek/kezelések, stb.), eredmények, megbeszélés, irodalom kell tagolni. *Esetismertetés* esetén a közleményt bevezetés, esetismertetés, megbeszélés és irodalom részekre bontsuk. *Minden más esetben* a közlemény felépítését a szerzők választják meg. Az irodalmi hivatkozások azonban mindig a közlemény végére kerüljenek.

Irodalom. Az irodalom idézése a szövegben zárójelbe tett arab számokkal történjen a hivatkozás előfordulásának sorrendjében, és nem abc szerint. A szövegben a szerzők nevét dőlt betűvel írjuk, ilyenkor a vonatkozó szám a szerző neve után jön. Ha a szerző neve nem szerepel a mondatban a hivatkozási szám a mondat végére, de még a pont elé kerül. A pont után a hivatkozási számot csak akkor kell tenni, ha az az egész bekezdésre vonatkozik. Az irodalmi adatokat az „irodalom" részben, amely a szöveges rész után következik, az idézés sorrendjében írjuk az alábbiak szerint.

Folyóirat és különszám

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Könyv

László J, Gaál M. Nőgyógyászati pathológia. 2. kiadás, Budapest, Medicina Könyvkiadó. 1976:33.

Könyv fejezet

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Az irodalmi hivatkozások pontosságáért a szerzők felelősek. Ha a szerzők száma hat vagy annál kevesebb, az összes szerző nevét soroljuk fel. Ha hatnál több, csak az első hatét és utána az „és mtsai" (idegen nyelvű közlemény esetén „et al") kifejezést írjuk. Egyszavas folyóiratok nevét teljesen ki kell írni, egyébként a folyóiratok nemzetközileg elfogadott rövidítéseit, amelyet az **Index Medicus** tartalmaz, alkalmazzuk. A Nőgyógyászati Onkológia rövidítése: Nőgyógy Onkol.

A köszönetnyilvánítást az irodalom után írjuk.

Oldalszámozás folyamatos, a címoldal az első oldal.

Táblázatok. A szövegben a táblázatok számozását megjelenésük sorrendjében, zárójelbe tett arab számokkal írjuk pl. *(1. táblázat, Table 1)*. A táblázatokat, a táblázat felett megszámozva külön oldalakon kérjük. A számozás után a táblázat címe következik. A táblázat alá rövid magyarázó szöveg kerül. Ide írjuk megfelelő jelöléssel a táblázatban előforduló rövidítések magyarázatát is. Más szerzőktől vett táblázatok csak az eredeti szerzők vagy a szerzői jog tulajdonosának engedélyével idézhetők.

Ábrák. Mindig az eredeti ábrákat, fényképeket kell beküldeni két példányban. A szövegben az ábrák számozását megjelenésük sorrendjében, zárójelbe tett arab számokkal írjuk pl. *(1. ábra, Figure 1)*. Az ábrák hátoldalán vékony ceruzával vagy ragasztható cédulán tüntessük fel a sorszámot, a szerző nevét és az ábra irányát kis nyíl segítségével. Kontrasztos, jó minőségű fekete-fehér fényképeket kell küldeni. Szükség esetén azonban színes képet is elfogadunk. A rajzolt ábrák fekete tintával fehér háttér előtt készüljenek. Az ábra aláírásokat külön lapon kérjük. Ebben az ábrán használt jelzések magyarázatát is adjuk meg. Más szerzőktől vett ábrák csak az eredeti szerzők vagy a szerzői jog tulajdonosának engedélyével idézhetők. A beküldött ábrákat csak a szerzők külön kérésére küldjük vissza.

Mértékegység. A mértékegységeket „méter rendszerben", SI egységekben kell megadni.

Rövidítések. A rövidítéseket a szövegben először jelentésük teljes kiírása után zárójelben adjuk meg, és csak ezután használjuk önállóan.

Helyesírás. Törekedjünk magyar orvosi kifejezések használatára, az idegen kifejezéseket, amikor csak lehet, kerüljük el. (Az orvosi kifejezések magyarosítása kívánatos.) Nem magyar eredetű szavak írása az eredeti írásmód szerint történjen. Magyaros helyesírással csak a köznyelvben meghonosodott (pl. krónikus, akut) szakkifejezéseket írjuk. Egyazon közleményben következetesen kell alkalmazni a magyaros vagy klasszikus írásmódot. Angol nyelvű szövegben az angol és az amerikai helyesírás is alkalmazható.

CÉLKITŰZÉS ÉS INFORMÁCIÓ A **Nőgyógyászati Onkológia** a Magyar Nőgyógyász Onkológusok Társaságának hivatalos lapja. Azzal a céllal jött létre, hogy a nőgyógyászati onkológiának, a szülészet-nőgyógyászat és az onkológia önálló szakmájának, hazánkban is tudományos fórumot teremtsen. Nőgyógyászati onkológiai folyóirat más országokban és nemzetközi szerkesztésben már évtizedek óta létezik, ezért a **Nőgyógyászati Onkológia** megjelentetése az orvostudománynak ezen a területen a haladó világhoz történő felzárkózásunkat jelenti. A szakmai célkitűzések mellett a magyar orvosi nyelv művelése, jobbítása is a lap alapvető feladata.

A **Nőgyógyászati Onkológia** a női nemiszervek, az emlők és a határterületek daganatos megbetegedéseivel, valamint az ezekhez kapcsolódó általános, elméleti és gyakorlati kérdésekkel foglalkozik. Tárgyalja továbbá a nőgyógyászati onkológiát, mint szakmát, beleértve a szervezési, a képzési és anyagi meggondolásokat is. A lap eredeti, összefoglaló és szerkesztőségi közleményeket, eset ismertetéseket és beszámolókat közöl. Különös hangsúlyt fektet a képzésre, amelyet nemcsak elméleti, de gyakorlati szinten is meg kíván valósítani. Orvostörténeti ismertetéseket ad annak tudatában, hogy nincs jelen és jövő a gyökerek ismerete nélkül. Társasági hírek, kritikák, megemlékezések, események ismertetése és más hírmondás a folyóiat szerves részét képezik. Határterületi kérdések és beteg tájékoztatók szintén a célkitűzések közé tartoznak. A **Nőgyógyászati Onkológia**, mint a Magyar Nőgyógyász Onkológusok Társaságának hivatalos lapja, a Társaság állásfoglalásait, hír-leveleit és más kiadványait közli.

A felkért közlemények kivételével minden közleményt két bíráló véleményez. Ennek alapján a **Nőgyógyászati Onkológia** is az ún. „bírálóan átnézett" (peer-reviewed) folyóiratok közé tartozik. A bírálók javaslatot tesznek módosításokra és a közlemény elfogadására vagy elutasítására, amelyet a szerkesztőség messzemenően figyelembe vesz. A bírálók személyét nem fedjük fel. **A közleményekben megfogalmazott vélemények, javaslatok nem a szerkesztőség, hanem a szerzők véleményét, állásfoglalását jelentik.**

A **Nőgyógyászati Onkológia** alapvetően magyar nyelvű. A kis népek létezése azonban megköveteli a kétnyelvűséget, ezért a lapban a közlemények összefoglalóját és a fontosabb adatokat angol nyelven is ismertetjük. Elfogadunk angol nyelvű közleményeket, egy-egy nemzetközi rendezvény előadásait pedig teljes egészében angolul adjuk közre.

SCOPE AND INFORMATION With the rapid advances of radical surgery, clinical technologies, anasthesia, modern blood banks, antibiotics, medical oncology and radiotherapy, and with the explosion of molecular biology it has been recognized that the usual training of gynecologists-obstetricians was insufficient to provide optimal care for patients with malignancies of the female genital tract and breast cancer. This recognition has led to the development of the subspecialty of gynecologic oncology with board certification in many countries worldwide.

Since the establishment of our specialty, a plethora of information has been accumulated with the recognition that in the rapidly expanding field of gynecologic oncology it is becoming almost impossible to be up-to-date with issues of concern. The spectrum of gynecologic oncology is broadening each day and includes among others advanced surgery, fundamental understanding and practice of drug- and radiation therapy and an in-depth knowledge in pathology and molecular biology. The gynecologic oncologists should keep pace with these exciting basic and clinical advances. The explosion of scientific information brought about by molecular and cellular biology should be reflected in patient's care at bedside. Cancer treatment and molecular biology cannot be separated any longer. These are some of the major reasons of establishing national and international journals devoted to gynecologic oncology.

In Hungary, gynecologic oncology has been officially recognized as a specialty of obstetrics and gynecology. This was followed by the foundation of the Hungarian Society of Gynecologic Oncology in 1991. During the last 5 years, there has been a growing need for a national venue for publications focusing on clinical and basic gynecologic oncology. Thus, the foundation of the **Hungarian Journal of Gynecologic Oncology** with the aim of providing a sole forum for gynecologic oncology in Hungary. The **Hungarian Journal of Gynecologic Oncology** is the official journal of the Hungarian Society of Gynecologic Oncologists.

The **Hungarian Journal of Gynecologic Oncology** will provide a national archive to high quality papers that deal with tumors of female genital tract and related organs, and with the benign and malignant diseases of the breasts. Reports of investigations relating to any aspect of these fields, including etiology, epidemiology, pathology, diagnosis, treatment, follow-up and basic science will be considered. Such contributions may come from any of the disciplines with interests in gynecologic oncology.

The **Hungarian Journal of Gynecologic Oncology** will publish original articles, invited reviews, brief reports, papers focusing on the history and on the professional aspect of the specialty, news, comments, critique, book reviews and letters. Education with particular emphases on continuing medical education is one of the major aims of the journal.

The language of the **Hungarian Journal of Gynecologic Oncology** is basically Hungarian. However, paper written in English will also be accepted.

The original manuscript together with a coverage letter must be submitted to the Editor-in-Chief (Péter Bősze, M.D. 1301 Budapest, P.O. Box 46, Hungary. Tel/fax: (36-1) 275-2172, E-mail address: bosze@mail.matav.hu). The authors are encouraged to E-mail their manuscripts or submit the article on a disk with adequate labelling and information (3 1/2 diskette in IBM MS-DOS). In either case an accurate hard-copy print-out must accompany. The Editor-in-Chief requires the original manuscripts and the cover letters. By signing the cover letter, the authors certify that the same work has not been published, that it is not under consideration for publication elsewhere, that its submission for publication has been approved by all of the authors, and that any person cited as a source of personal communications has approved such citation. By signing the cover letter, the authors transfer the copyright to the Publisher. Manuscript decisions will be based on peer review.

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