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 Since the sixties Radium has gradually been replaced by artificial radionuclides (Cobalt-60, Caesium-137 and Iridium-192) and direct insertion of radioactive sources – by manually or remotely controlled afterloading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.

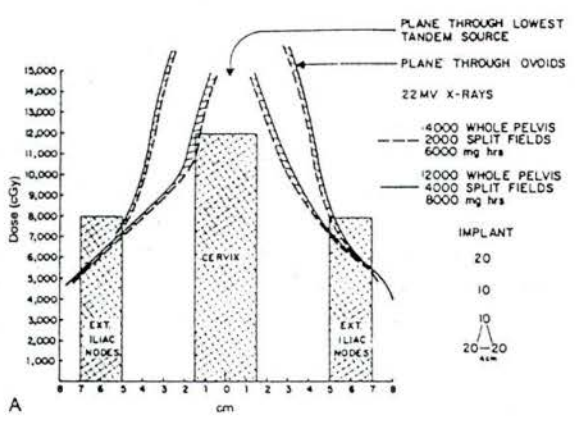
Patients with less advanced stages (IB, IIA and IIB with proximal infiltration of parametrium) can be treated either by combination of surgery and radiotherapy or exclusive radiotherapy. Numerous uncontrolled studies support the merits of either modality but therapeutic decision can sometimes be controversial 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)*).



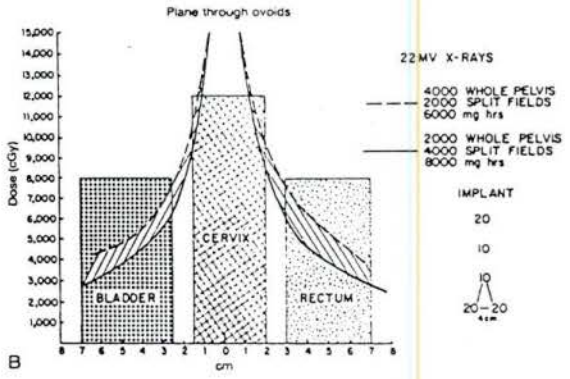


Figure 1. Dose profiles in the coronal (A) and sagittal (B) planes for patient with carcinoma of the uterine cervix treated with 2000 cGy to the whole pelvis and 8000 mgh or 4000 cGy to the whole pelvis and 6000 mgh. Additional dose to the parametria is delivered to complete 6000 cGy. The dose distributions 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)).

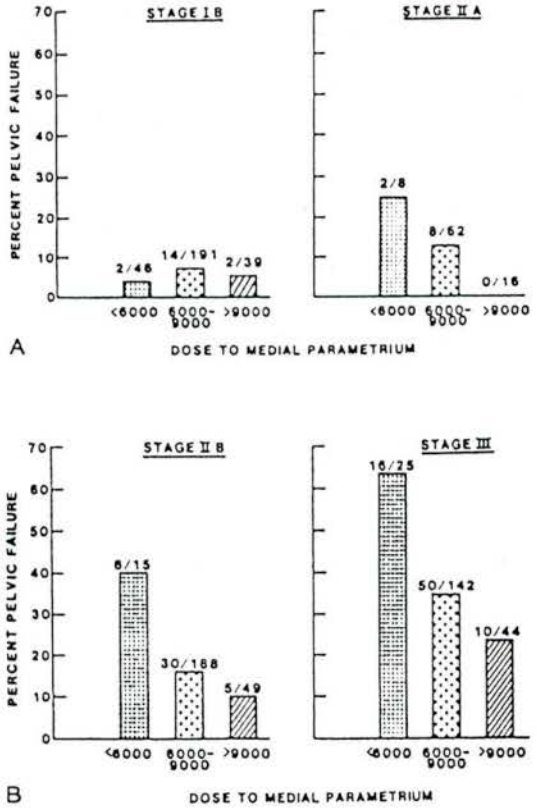


Figure 2. (A and B) Local/marginal parametrial recurrences correlated with dose to medial parametrium (0.8) in patients with stage IB, IIA, IIB, or III carcinoma of the uterine cervix. Decreasing parametrial recurrences are noted with higher doses of irradiation in stage IIA and greater. (Perez CA, et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