# Exclusive radiotherapy in the management of endometrial carcinoma

ANNA KOBIERSKA M.D.[1], ALAIN P. GERBAULET, M.D.[2]

*Department of Oncology and Radiotherapy,[1] Gdansk Academy of Medicine, Gdansk*
*Department of Brachytherapy,[2] Institut Gustave-Roussy, Villejuif*

**INTRODUCTION** The generally accepted management for early stages of endometrial carcinoma is surgery (total abdominal hysterectomy and bilateral salpingo-oophorectomy with paraaortic 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).

*Address correspondence to:*

**Anna Kobierska, M.D.**
Department of Oncology and Radiotherapy
Gdansk Academy of Medicine
80-211 Gdansk, ul. Debinki 7.
Phone (48 58) 322916 Fax (48 58) 322916
E-mail onkol@amed01.amg.gda.pl

**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.

**REFERENCES**

1. Gerbaulet A, Blondeau L, Lusinchi A, Haie-Meder C, Habrand JL, Chassagne D, Castaigne D, Rahat T, Michel G, Duvillard P, Prade M. Endometrium carcinoma. General indications of LDR brachytherapy. Institute Gustave – Roussy Experience. ESTRO Teaching Course on modern brachytherapy techniques, Athens, 1993.

2. Stokes S, Bedwinek J, Perez CA, Camel HM, Kao MS. Hysterectomy and adjuvant irradiation for pathologic stage III endometrium carcinoma. Int J Radiat Oncol Biol Phys 1986; 12:335.

3. Hacker NF. Uterine cancer. In: Berek JS, Hacker NF, eds. Practical Gynecologic Oncology. Baltimore, Williams and Wilkins, 1994.

4. Perez CA, Knapp RC, Disaia PJ, Young RC. Gynecologic tumors. In: DeVita VT, ed. Principles and Practice of Oncology 2nd edn. 1985.

5. Grigsby PW, Perez CA. Intracavitary and external beam irradiation for endometrial carcinoma. Brachytherapy 2. Nucletron Int BV, 1989; 38:252-267.

6. Perez CA, Purdy JA. Biologic and physical aspects of radiation oncology. In: Hoskins WJ, Perez CA, Young RC, eds. Principles and Practice of Gynecologic Oncology, 1992.

7. Henschke U. Afterloading applicator for radiation therapy of carcinoma of the uterus. Radiotherapy 1960; 74:834.

8. Pernot M. Radiation therapy alone for the treatment of endometrial carcinoma. ESTRO Teaching Course on modern brachytherapy techniques, Athens, 1993.

9. Potter R, Knocke TH. HDR-brachytherapy in endometrium carcinoma. ESTRO Teaching Course on modern brachytherapy techniques, Athens, 1993.

10. Rotte K. Technique and results of HDR afterloading in cancer of the endometrium. Brachytherapy HDR and LDR. Nucletron Int 1990; 68-79.

11. Herbolsheimer M, Sauer, Rotte K. Primary irradiation of endometrial cancer. Endocurieth Hypertherm Onkol, 1992; 8:11-18.

12. Maruyama Y, Van Nagell JR, Yoneda J, DePriest P, Kryscio RJ. Clinical evaluation of Cf-252 neutron intracavitary therapy for primary endometrial adenocarcinoma. Cancer 1993; 71:3932.

13. ICRU Report No. 38. Dose and volume specification for reporting intracavitary therapy in gynecology, 1985.

14. Kupelian PA, Eifel PJ, Tornos C, Burke TW, Delclos L, Oswald MJ. Treatment of endometrial carcinoma with radiation therapy alone. Int J Radiat Oncol Biol Phys 1993; 27:817.

15. Lehoczky O, Bősze P, Ungár L, Töttössy B. Stage I endometrial carcinoma: treatment of nonoperable patients with intracavitary radiation therapy alone. Gynecologic Oncology 1991; 43:211.

16. Taghian A, Pernot M, Hoffstetter S, Luporsi E, Bey P. Radiation therapy alone for medically inoperable patients with adenocarcinoma of the endometrium. Int J Radiat Oncol Biol Phys 1988; 15:1135.

17. Rouanet P, Dubois JB, Gely S, Pourquier H. Exclusive radiation therapy in endometrial carcinoma. Int J Radiat Oncol Biol Phys 1993; 26:223.