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 predefined groups, brachytherapy can be included in different protocols: combined with surgery and/or radiotherapy, brachytherapy alone and salvage brachytherapy.

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, 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 occurred 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.

**Stage II disease**
1. Vaginal or utero-vaginal brachytherapy (if endocervical involvement is important) immediately followed by surgery.
2. BSOH + external iliac lymphadenectomy and 3. Complementary external radiotherapy as for stage I.

In this combined radio-surgical treatment, several questions, however, remain to be answered:
- 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: myometrical 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 due 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)**

<table>
<thead>
<tr>
<th></th>
<th>Brachytherapy dose in Gy</th>
<th>Rectum</th>
<th>Bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vaginal</td>
<td>24</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>uterovaginal</td>
<td>29</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>37</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Surgical difficulties</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer invasion</td>
<td>1%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>2.5%</td>
</tr>
<tr>
<td>Miscellaneous reasons</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritonitis</td>
<td>1%</td>
</tr>
<tr>
<td>Ureterovaginal fistulae</td>
<td>2%</td>
</tr>
<tr>
<td>Lymphocysts</td>
<td>4%</td>
</tr>
</tbody>
</table>
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 allowing 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),
- Bloodorn-Delcos applicator,
- disposable Delouche applicator,
- Fletcher, Raynal, Baillet...

**WHAT DOSE TO GIVE** The ICRU recommendations for specification of absorbed dose and irradiated volume in intra-cavitory 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 mucusal 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 proproative, 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 administrated 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: grade 1 (1.6%), 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.

**SUGGESTED REFERENCES**


