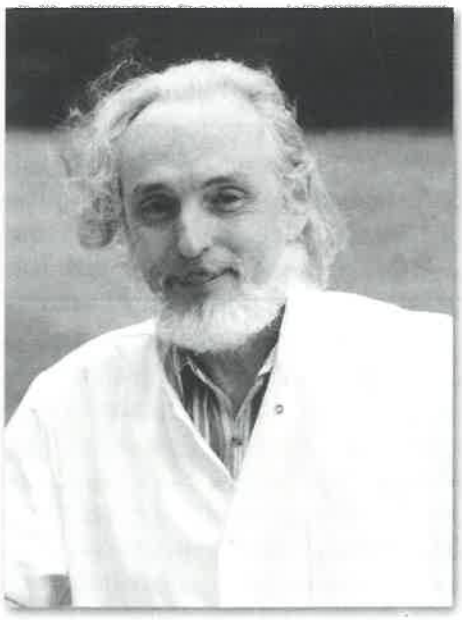
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Endometrial carcinomas: which radiotherapy for which patient?

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Summary

Endometrial cancer is the third most common malignancy in women. The endometrioïd adenocarcinomas represent 75% to 80% of the pathological subtypes. Ninety per cent of the lesions are stages I or II at diagnosis. Treatment strategies are based on surgery and radiotherapy, but the respective place of external irradiation and intracavitary brachytherapy is not strictly established. The role of pelvic lymphadenectomy and the role of chemotherapy for aggressive histologies or locally advanced disease remain also controversial issues. The question «which radiotherapy for which patient?» is still debatable. Hence, although the answers we will provide may clarify some issues, they will not remove all uncertainties.

Key words: endometrial carcinoma, external irradiation, vaginal cuff brachytherapy

Introduction

Endometrial cancer is the third most common cancer in women after breast cancer and colon cancer. Its incidence increases with age, the other risk factors being obesity, nulliparity, personal previous history of pelvic irradiation, family previous history of endometrial carcinoma, menopausal substitute treatments by exclusive oestrogenotherapy and tamoxifen. Endometrial carcinomas are usually revealed by postmenopausal metrorrhagia. Most patients (90%) are first seen with a lesion limited to the uterus (stages I and II). Endometrial adenocarcinomas represent 75% to 80% of the cases. The pathology grade of the lesion must be systematically documented by an experienced pathologist.

Endometrial adenocarcinoma has been long considered as a cancer of local malignancy, which explains why hysterectomy or intra-uterine brachytherapy according to Heyman's technique [1] have remained the two treatment references till the beginning of the 70's. The analysis of the results of these treatments and the identification of the prognostic factors allowed a better knowledge of the evolution of the disease (50% locoregional failures and 50% metastatic failures) and led to pluridisciplinary management. Surgery is the initial treatment in most cases. Adjuvant treatment relies on external radiotherapy and on vaginal brachytherapy to prevent lateropelvic nodal recurrences and vaginal recurrences. The results of these strategies were mostly evaluated by retrospective studies and the few prospective studies do not provide at present time a better evidence level than the knowledge accumulated thanks to historical and empirical experiences with a considerable number of patients.

The three main controversial subjects are the role of lymphadenectomy at initial surgery, the respec-

tive role of external radiotherapy and vaginal brachytherapy and, finally, the potential interest of the use of chemotherapy to prevent metastatic evolution in high risk presentations. Then, the question "which radiotherapy for which patient?" remains of interest in 2004.

Therapeutic strategies

Surgery

Whatever the initial stage of the disease, the choice of the therapeutic strategy is exclusively based on the patient's operability. Indeed, upfront radical surgery is considered as a standard in most countries. Present consensus only gives a limited optional role to preoperative radiotherapy strategies in some stage II cases. Patients non-operable for medical reasons or patients having unresectable cancer are benefiting from radiotherapy alone.

Initial surgery is the best method to perform a precise staging, to gather prognostic information and to ensure locoregional control for lesions limited to the endometrium and even for low-grade lesions with superficial invasion of the myometrium. The procedure starts with an abdominal exploration and a peritoneal washing. Extrafascial hysterectomy combined with bilateral oophorectomy is the reference technique. Vaginal hysterectomy is acceptable only when abdominal hysterectomy is not feasible. Surgery extended to the parametria can be discussed for stages II (with gross extension to the endocervix). Surgery with omentectomy is advisable for stage III with spread to the tubes and ovaries and in serous papillary carcinomas. On the other hand, the usefulness of lymphadenectomy remains controversial. Its interest is indisputable in the case of macroscopic nodal spread. In the other cases, the absence of therapeutic benefit being well documented, the purpose of lymphadenectomy is limited to the identification of the subgroup of patients who will benefit from an adjuvant treatment. However, several studies clearly established that histoprognostic factors were all closely correlated. Hence, a positive lymphadenectomy is often combined with the existence of other poor prognostic factors [2,3]. Lymphadenectomy would only provide discriminating information in the group of patients with a low risk for recurrence, which would occur with a very low probability: the analysis of the GOG 33 trial showed that the percentage of nodal invasion is less than 10% [4]. The argument of morbidity of the procedure is also an important argument against systematic lymphadenectomy: it increases the risk for peri-operative complications, increases the duration of hospital stay and multiplies by 4 the risk of late complications when adjuvant radiotherapy must be given post-operatively [5-8]. Although the Fédération Internationale de Gynécologie Obstétrique (FIGO) advises pelvic lymphadenectomy, the French SOR (Standards, Options & Recommendations) only support it if easily feasible in patients in good general condition, who do not present prognostic factors necessitating adjuvant external radiotherapy [9].

Adjuvant treatment

The indication of adjuvant treatment relies on the analysis of prognostic factors, which, for most of them, can be determined reliably only on the pathology specimen. These are the stage (depth of myometrial invasion, spread to endocervix, pelvic nodes), the histologic type (endometrioïd *versus* serous papillary or clear cell), the histopathological prognostic grading (G1 G2 *versus* G3), the positivity of the peritoneal cytology and the presence of vascular embolisms [10]. Age over to 60 or 70 years, according to series, is also described as a factor of bad prognosis; however, the indication of an adjuvant treatment cannot rely on this factor only [10-12].

At present, radiotherapy is the only adjuvant treatment that is really efficient to improve the results of the local control of endometrial carcinoma with poor prognostic factors. Respective indications for external radiotherapy and brachytherapy need to be carefully discussed. Trying to answer the question "Which radiotherapy for which patient" considering only adjuvant treatment is certainly too restrictive because it deprives us of an historical experience which feeds the controversy and helps finding the proper answer for the individual patient.

Which radiotherapy for which patient? Stages I and II

Stage I are lesions limited to the uterine body only (IA endometrium alone, IB penetration in the myometrium ≤50%, IC penetration in the myometrium >50%), and stage II when there is extension to the endocervix (IIA superficial infiltration, IIB with chorion invasion).

Postoperative external radiotherapy

The interest of postoperative external radiotherapy was assessed by three randomized clinical trials

[11,13,14]. Aalders' et al. study, led at the end of the 70's, was too old to be considered with reliable conclusions. However, it deserves credit for demonstrating for the first time that external radiotherapy allowed to reduce local recurrences in stage I (6,9% in the Surgery-chemotherapy (CT) arm against 1.9% in the Surgery-CT-Radiotherapy arm) and that only patients with grade 3 or stage IC tumours really benefited from external irradiation. No impact on survival was revealed [13]. The 80's and the beginning of the 90's were marked by the publication of many retrospective studies confirming these results, with a decrease of the recurrence rates varying from 25% to 50% [7,15-17].

The two most recent randomized studies were led by the Gynecology Oncology Group (trial GOG 99) and by the PORTEC Study Group [4,14]. A trial similar to the PORTEC trial is in progress at present in the NCIC trials group. The target population was all the substages I for the GOG 99 trial, the substage IB G2/G3 and the stage IC G1/G2 for the PORTEC trial. After hysterectomy with or without lymphadenectomy the patients were randomized between external radiotherapy or no further treatment (50.4 Gy in the GOG 99 trial, 46 Gy in the PORTEC trial). The results are summed up in Table 1. The GOG 99 trial has only been published as an abstract and the follow-up is 3 years only. However, the two trials are tally to show that overall radiotherapy allows to significantly decrease the locoregional recurrence rate but has no impact on the metastatic evolution nor on survival. The actuarial 5-year complication rate in the PORTEC trial is significantly higher in the surgery-radiotherapy arm (26% among which 3% of severe complications) than in the surgery alone arm (4%). Considering toxicity and the lack of impact on survival, the investigators of these trials concluded that such an adjuvant treatment should be only recommended to patients whose recurrence probability rate was higher than 10%. The multivariate analysis of the PORTEC trial allowed to define this group of "high risk" patients as being the patients of more than 60 years old having stage IC grade 1-2, and the patients having grade 3 tumours whatever the age. The decision rules to prescribe an adjuvant external radiotherapy are more complex for GOG 99 investigators, depending on age and presence of one or several of the following prognostic factors: infiltration of the myometrium, grade 3, presence of vascular embolisms. Adjuvant external irradiation is advised in patients over 70 years old with only one factor, for patients over 50 years old with 2 factors and for all patients with the 3 factors.

Is vaginal brachytherapy necessary in addition to external radiotherapy?

The answer is given by the results of retrospective studies comparing adjuvant external radiotherapy alone to external radiotherapy followed by a vaginal brachytherapy delivering 40 to 50 Gy surface dose using low-dose rate, mainly for stage I [12,18-20]. Only one of these studies demonstrated a significant improvement of the local control rate [18], whereas all the series reported a significant increase of mild complica-

Table 1. Comparison of GOG 99 and PORTEC trials

	GOG 99		*PORTEC*	
Inclusion criteria	All stages I		IB G2/G3, IC G1/G2	
Study scheme	Hysterectomy + Lymphadenectomy then ERT 50.4 Gy vs nothing		Hysterectomy alone then ERT 46 Gy vs nothing	
Characteristics of the patients included	390 patients IB 70%, G1/G2 82%		790 patients IB 39%, G1/G2 90%	
Recurrence rate (%) (2 years GOG, 5 years PORTEC)	SURG 10	SURG + ERT 1.5	SURG 14	SURG + ERT 4
Survival (%) (2 years GOG, 5 years PORTEC)	SURG 89	SURG + ERT 96	SURG 85	SURG + ERT 81
Failure sites (%)	SURG	SURG + ERT	SURG	SURG + ERT
Vagina	9	1	10	2
Pelvis	5	0	3	2
Metastases	7	6	4	6

ERT: external radiotherapy

tions (mostly upper vaginal fibrosis). We have no similar information with high-dose rate brachytherapy, but it is very unlikely that the outcome would be different.

On the other hand, the deep invasion of the endocervix (stage IIB) is an argument to systematically perform a vaginal brachytherapy to the vault after external radiotherapy [21].

Vaginal brachytherapy alone

Analysis of the locoregional failure sites after surgery showed that the majority of recurrences are vaginal recurrences and that their incidence varies from 8% to 15% according to the series. Prospective trials showed that external radiotherapy could prevent them with some risk of pelvic toxicity (mostly to small bowel, bladder and soft tissues). This led us to consider the opportunity to treat only the vaginal cuff. The results of numerous retrospective series confirm that brachytherapy alone is sufficient to prevent vaginal recurrences in most situations without significant late toxicity.

Postoperative vaginal brachytherapy alone is at present already considered standard by many multidisciplinary groups for stage IA grade 3 and for stage IB grade 1 and 2. In 2000, Pearcey and Petereit reported the results of a compilation of all the retrospective studies published in the past 30 years when vaginal brachytherapy was the only adjuvant treatment realized on patients with low or intermediate risk stage I. The vaginal recurrence rate in the 1,800 studied patients was 0.7%, which pleads in favour of adjuvant vaginal brachytherapy alone in these indications [22]. The results of Alektiar et al. series (233 stage IB G1/2) reached the same conclusion since the results of the local control, of survival without recurrence and of complications at 5 years were 96%, 94% and 2%, respectively [23].

The results of high-dose rate vaginal brachytherapy alone in patients with a high risk of recurrence (IC grade 1-2, IB/IC grade 3, IIA) without nodal spread (compulsory lymphadenectomy) are also interesting because the recurrence rates range between 0% and 10% [24-31]. However, these series are not always comparable since, in some of them, the small number of patients does not allow to state with confidence that adjuvant vaginal cuff brachytherapy alone is an alternative to external radiotherapy for patients with a high risk. The PORTEC Study group has just started a new trial who should answer that question in stages IB G3 and IC G1-G2. This study compares external radiotherapy to a vaginal brachytherapy. PORTEC2 trial is recording quality assurance of the treatment planning and parameters to minimise the late toxicity rate compared with the PORTEC1 trial.

Is there still a place for pre-operative radiotherapy?

Preoperative radiotherapy strategies were given up by most of the teams at the end of the 80's because of the difficulty to appreciate the prognostic factors in a preoperative setting. However, it can be argued that the results of the fractionated curettage, which can be made during the assessment phase, are able to provide the 3 main prognostic factors: pathology, grading and depth of myometrial invasion. T2 MRI sequences with gadolinium injection allow to appreciate the depth of the myometrial infiltration with a 90% sensitivity 85% specificity [32,33].

The role of preoperative utero-vaginal brachytherapy alone is no longer discussed, because controlled studies, even old, demonstrated it did not improve local control and survival compared to postoperative vaginal brachytherapy [22,34,35]. The strategy of external radiotherapy – preoperative brachytherapy has also been compared to the same strategy in the postoperative setting when treating stage I: here again the preoperative strategy does not seem to bring anything even in terms of toxicity (85% 5-year survival, 4% of severe toxicity) [36,37]. The results of the Dijon series give a new interest to this preoperative strategy in the stage I grade 3, because the local control observed in these patients with a high risk of recurrence is 100% [38]. The combination of external radiotherapy – preoperative brachytherapy for stage IIB has, on the other hand, an indisputable role even if few teams still do it. The results in survival are of about 80% at 5 years, which is far more superior to the 67% of the statistics of the FIGO international survey, which expresses the results of postoperative adjuvant radiotherapy [1,38,41]. The Dijon series also reports a local control rate of 100% in the 62 stage II patients treated by this method with a rate of severe complications of only 3% [38]. This raises the problem of the need for multidisciplinary expertise in these high risk cases: when present in the fields of pathology, imaging, radiotherapy (including brachytherapy) and surgery, results better than average can be obtained by proper selection of patients, individualisation of management without exposing these often fragile patients to a higher rate of late complications.

Which radiotherapy for which patient? Stage III

Less than 15% of endometrial carcinomas are diagnosed with stage III. Consequently, the treatment recommendations rely only on retrospective studies with few patients. This mixed group of tumours includes lesions localized to the uterus with positive

peritoneal cytology, nodal spread, as well as localized vaginal metastases or massive abdominal extensions. Greven et al. perfectly demonstrated that survival without recurrence was correlated by the number of involved sites [42]. Survival is also significantly better when stage III is a microscopic stage than when there is macroscopic tumour extension [43,46]. Surgical resection must be suggested to every operable patient because the survival rates vary from 30% to 60% in operated patients compared to 20% only in patients treated exclusively by radiotherapy. Postoperative radiotherapy is practically always prescribed.

The problematic issue of the postoperative treatment of stage III is the volume to be irradiated. A pelvic irradiation combined to brachytherapy is adapted to most situations for 1) Unilateral tube invasion from a primary with no deep myometrial invasion, 2) Vaginal spread, 3) Lesions limited to the uterus with positive pelvic nodes alone. Pelvic radiotherapy extended to para-aortic nodes is recommended when nodal spread is documented (surgery and/or imaging) on iliac nodes and/or peri-aortic nodes and can be discussed in case of multiple pelvic nodes invasion in patients in good general condition. Total abdominal irradiation is a logical treatment for tubes and ovaries spread combined with poor prognostic factors (e.g. grade 3) and/or positive ascites. Its interest is questioned in the case of isolated positive peritoneal cytology. Most teams agree that the pejorative value of an isolated positive peritoneal cytology for tumours confined in the uterus is not demonstrated and that this factor can be neglected and a classical therapeutic strategy can be suggested for stages I and II [47-50]. Spread to multiple pelvic sites, whose evolution is closer to (and sometimes difficult to differentiate from) ovarian carcinomas should in principle benefit from total abdominal irradiation. However, literature reports are scarce and do not provide a strong basis for this indication. The potential interest of adjuvant chemotherapy alone for these massive or multiple pelvic spread has been studied in the framework of GOG 122 trial where chemotherapy with cisplatinum and adriamycin was compared to a total abdominal irradiation. Results are expected soon. The GOG 184 trial, which is still in progress, is asking the question of adjuvant chemotherapy after an abdominal irradiation.

Which radiotherapy for which patient? Pathological poor prognostic factors

Aggressive histological presentations are mainly made of clear cell carcinomas and serous papillary carcinomas. Clear cell carcinomas have a similar prognosis with endometrioïd carcinomas of grade 3, and must be treated as such. Serous papillary carcinomas are much more aggressive and are revealed as stage III in 62% of the cases. The optimal treatment is not known, the combinations of adjuvant radiotherapy and chemotherapy seem more efficient than radiotherapy or chemotherapy alone. The EORTC-GCG 55991-NSGOEC 9501 trial, comparing adjuvant sequential radiochemotherapy to adjuvant external radiotherapy in high-risk aggressive forms, is still in progress.

Which radiotherapy for which patient? The inoperable forms

Patients being inoperable for medical reasons or for unresectable tumours are treated with irradiation alone according to the same principles as irradiation alone of the uterine cervix cancers but with the additional concern to deliver a sufficient dose (70-80 Gy) to the uterine body. The stage I overall 5-year survival treated by radiotherapy alone varies from 60% to 70%, of stage II from 30% to 65% and of stage III is about 20% [51-53].

Which radiotherapy for which patient? The treatment techniques

It is advisable to deliver postoperative radiotherapy with the same care as radiotherapy with the uterus in place, in order to control the dose to the critical organs. The high morbidity of the PORTEC trial is partly explained by the technique of radiotherapy with AP/PA portals used for most patients. A 4 field-box technique is now the reference, with small bowel and bladder shielding based upon 3D imaging and treatment planning. The clinical target volume (CTV) includes the whole uterus and adnexae, upper part of the vagina, and pelvic nodes. Irradiation of the abdominal cavity is advisable only for selected stage III cases (cf supra). The margins, considering the uncertainties of positioning the planned target volume (PTV), must be of about 10 mm beyond the CTV, since the daily set-up of these often obese patients often creates problems of reproducibility. The use of quality control procedures of positioning, mainly with digital portal imaging, reduces considerably the risk of geographical miss. In case of preoperative radiotherapy or exclusive radiotherapy, a minimum margin of about 10 mm must be added to take into account the movements of the uterus. A dose from 40 Gy to 50 Gy is usually delivered. Vaginal

cuff postoperative brachytherapy is now often delivered with high dose rate (HDR) brachytherapy allowing an ambulatory treatment. Reference schemes are of 4×5 Gy or 4×6 Gy prescribed at 5 mm mucosal depth for brachytherapy alone, and of 2×5 Gy or 1×6.5 Gy for brachytherapy after external irradiation.

Conclusions

1. This lesson allows a simple decision tree in the following presentations:

– IA G1 G2: surgery alone.

– IA G3; IB G1 G2; IIA < 50% of the myometrium, G1 G2: surgery followed by vaginal brachytherapy.

– IIA <50% of the myometrium, G3; IIA > 50% of the myometrium, G2 G3; IIB; III: surgery followed by external radiotherapy and vaginal brachytherapy.

2. Controlled trials failed to demonstrate that postoperative external radiotherapy is of benefit for stages IB G3 and IC. At present, a trial similar to the PORTEC trial has been conducted by the NCIC clinical trials group. Relevant questions, however, are investigated by the PORTEC2 trial (still in progress): external radiotherapy *versus* vaginal vault brachytherapy.

3. The question remains unsolved for patients with massive endocervical invasion (stage IIB). Most teams still recommend a classical strategy "surgery followed by external radiotherapy and brachytherapy" while others (including us) have reported series with preoperative strategy suggesting better results in terms of local control and survival and less complications. This could be a good topic for a large phase III trial which unfortunately would be hardly feasible for methodological reasons.

4. The present indications of adjuvant treatment are mainly based on tumor staging and the histoprognostic grading without taking into account the two other independent prognostic factors, which are age and the presence of vascular embolisms. The decision rules of adjuvant treatment according to age, suggested by the PORTEC Group and by the GOG, do not seem to be sufficiently supported to be used as standards. Also we do not have any data allowing to define the optimal management in case of vascular embolisms. Research studies are needed to evaluate the various choices proposed.

5. The other pending questions are what to do in case of isolated positive peritoneal cytology, and optimal treatment management of stage III and aggressive histologies. The rareness of some situations (isolated peritoneal cytology: 5% of the cases) will not allow other answers than those brought by retrospective studies. At present, trials are in progress to measure the impact of chemotherapy on the results of aggressive forms and locally advanced stages.

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