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# Adjuvant radiotherapy in Stage I endometrial cancer. Where do we stand?

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**Summary**

This paper reviews the anatomical spread and failure patterns of surgical Stage I endometrial cancer. The controversial aspects of the optimal adjuvant treatment are presented. An attempt is made to identify the most effective management approach based on the pertinent literature data.

*Key words:* Stage I endometrial cancer; Risk factors; Lymphadenectomy; Adjuvant radiotherapy.

## Introduction

The incidence of endometrial carcinoma has increased in recent years, especially in developed countries, and now exceeds the incidence of carcinoma of the cervix in several developed countries. Most commonly it occurs in postmenopausal women (75-80%), between the ages of 55 and 60. It represents almost 50% of all female genital cancers and about 10% of all malignancies in women. Endometrial cancer is a highly curable cancer because about 80% of these tumours are diagnosed at Stage I, i.e., confined to the uterine corpus.

Surgery is the mainstay of therapy for endometrial carcinoma. This approach has become the standard of practice in most countries because of the accuracy of surgical-pathological staging data, and because the application of adjunctive postoperative radiation therapy can be selective. Radiation therapy either of the pelvis or in combination with brachytherapy of the vaginal vault is often used after surgery. Nevertheless, considerable controversy exists regarding the mode of adjuvant radiation therapy (external and/or internal) and the real effect of this therapy.

## Anatomical patterns of spread

Primary endometrial cancer begins as a surface growth that may extend to involve a greater proportion of the endometrial surface and ultimately spread to the lower uterine segment and cervix. Invasion into the myometrium may precede inferior spread. Once the tumour penetrates the myometrium, and especially when it reaches the lymphatic-rich subserosa, spread via lymphatic embolization is common.

Lymphatic spread varies with the site of uterine involvement. The lymphatic network of the uterine fundus follows the ovarian and the infundibulo-pelvic ligaments to the external iliac and para-aortic nodes. The corpus and isthmus is drained via the broad ligament to the obturator and iliac nodes. Endometrial carcinomas in the tubal corners of the uterus can spread via the round ligament to the inguinal (very rarely) and external iliac nodes. Tumour cells can also be sloughed through the tube into the abdominal cavity, although the prognostic significance of these cells in patients with disease limited to the uterus is unclear [1].

## Factors predicting lymph node spread

In order to identify patient subgroups at high risk for lymph node metastases the Gynecologic Oncology Group (GOG) performed a large-scale prospective surgical staging study on 621 patients with clinical Stage I endometrial cancer [2]. All patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy and the procurement of peritoneal fluid for cytological assessment.

The most relevant finding was that outer-third invasion of the myometrium and grade 3 histology tumours carry the highest risk for positive pelvic lymph nodes: 25% and 18%, respectively. For grade 2 and middle-

third myometrium invasion the relative frequency of positive pelvic nodes decreased to 8.6% and 6%, respectively. In their analysis, patients with endometrial adenocarcinoma can be classified into three risk groups according to the histological grade and myometrial invasion [2, 3].

Patients in the *low-risk* group (superficial invasion and grade 1) have a very low risk of pelvic or para-aortic node metastases.

Those in the *intermediate-risk* group (inner one-half invasion and grade 2) have a 3% to 6% risk of pelvic nodal involvement and a 2% risk of para-aortic metastases.

*High-risk* patients (outer one-half invasion, grade 3, extrauterine disease) have an 18% to 61% risk of pelvic nodal metastases and an 8% to 30% risk of para-aortic nodal involvement.

Other important predictors of lymph node involvement include histological type other than adenocarcinoma, lower uterine segment/cervical involvement, tumour size greater than 2 cm, adnexal metastases, and presence of any palpably suspicious lymph nodes.

Shortly after the publication of the GOG study the FIGO reclassified the staging system for endometrial cancer (1988) and since then, endometrial cancer has been surgically staged. However a new issue was brought forward by this procedure: the indication and the type (sampling/systematic) of lymphadenectomy that should be performed. The results of lymphadenectomy could substantially influence the decision to use adjuvant radiation therapy.

## Lymphadenectomy in the staging of endometrial cancer

Techniques for evaluating the true status of the pelvic and para-aortic lymph nodes in clinical Stage I patients were described by Chuang *et al.* [4]. Their opinion was that a limited assessment of the pelvic and para-aortic lymph nodes, a *selective lymphadenectomy*, in which about *ten nodes* were removed, accurately reflected the true nodal status. The nodal groups sampled were the common iliac, external and internal iliac, obturator and para-aortic on either side. This procedure is also referred to in the literature as *sampling* or *staging* lymphadenectomy although the number of the excised lymph nodes can vary according to the surgeons` and pathologists` technique.

Another approach is to perform lymphadenectomy with therapeutic intent [5]. In this approach all lymph nodes around the aorta and pelvic vessels are removed such that these vessels are left completely skeletonized. This procedure is called *systematic* or *extended* lymphadenectomy. The number of lymph nodes assessed is related to the technique of the pathologist who performs the examination. The median number of lymph nodes resected in the pelvis varies from 14-48 [5-9] and the median number of aortic nodes resected varies from 6-27 [6-9]. However most authors do not define a clear-cut line between the two kinds of procedures in terms of the number of lymph nodes excised being content with the term of "adequate" number of lymph nodes.

## Can a lymphadenectomy select patients who do not need radiation?

In a review on the staging and therapeutic value of lymphadenectomy, Podratz *et al.* conclude that only patients with documented positive pelvic node metastases should receive adjuvant pelvic external beam radiotherapy (AP-EBRT) [10]. They refer to a series of retrospective reviews [5, 11-13] that investigated patients at intermediate and high risk for recurrence but with negative pelvic nodes who received only vaginal vault radiation. The rate of local recurrences among 305 patients investigated in these reviews was 1.6%. However Morrow *et al.* writing about GOG Protocol #33, stated: "A negative staging laparotomy does not de facto identify a patient who needs no further therapy" [3]. This was a non-randomised study where the patients underwent a staging/selective lymphadenectomy. Among the 895 patients included in the final analysis, 148 patients (16.6%) were pelvic node positive and 48 (5.3%) were aortic node positive. Vaginal and pelvic recurrence rates were 34.6% for patients with greater than one-third myoinvasion and grade 2 or 3 tumours who did not receive AP-EBRT. Thus a selective lymphadenectomy does not seem to avoid the need for AP-EBRT. Petereit in his review on surgical staging in endometrial cancer concludes likewise [14]. He favours selective lymphadenectomy, a procedure that should be done in case of high-risk carcinoma features. However, at the present, paradoxically the outcome of lymphadenectomy does not seem to have an impact on the indication of adjuvant radiotherapy as most radiation oncologists do recommend AP-EBRT for patients with negatively staged lymph nodes who have grade 3 or deeply invasive tumours [15, 16]. Further randomised studies are needed to specify what the extent of the lymphadenectomy should be on the one hand and what the efficacy of this procedure is to determine the minimally effective adjuvant treatment on the other hand. Unfor-

tunately the experience emerging from lymphadenectomy has not led to a more sophisticated pelvic lymph nodal target volume definition. The reasons are the following: the staging studies in moderate- and high-risk endometrial cancer fail to give details about the number of lymph nodes assessed and/or the extent of the dissection; few investigators provide a detailed pattern of pelvic failure in their patients; most of the surgeons are labelling the lymph node specimens only as right or left pelvic lymph node group, omitting more specific lymph node group information so the anatomic distribution of metastases within the nodal groups can not be precisely analysed. Since the spatial extension of the clinical target volume (CTV) is mostly determined by the need to cover the entire pelvic lymph nodal areas at risk for involvement it would be essential to know the specific rates of metastatic involvement for different subgroups of pelvic lymph nodes in all stages of uterine cancer. Based on this knowledge only those lymph nodal areas would be included in the CTV that is at the highest probability of entanglement. Meanwhile until such data are available all the lymph nodes that belong to both the external iliac and the internal iliac lymph-nodal groups should be considered as CTV.

## The place of adjuvant radiation therapy in the management of Stage I disease

The need for radiotherapy as an adjuvant to surgery in Stage I carcinoma of the endometrium is controversial and is related to the lack of impact on overall survival. Preoperative radiotherapy has been replaced by appropriate postoperative radiotherapy as this allows full pathological assessment before deciding on the necessity for further treatment. Several clinical trials were conducted over the last decades in the search for the best radiation treatment modality for the various subgroups of Stage I endometrium carcinoma. These trials aimed to find out according to risk groups, whether the vaginal vault alone or the vaginal vault together with the pelvic lymph nodes should be irradiated. A summary of the relevant data from trials that employed AP-EBRT and vaginal brachytherapy (VBT) follows.

### 1. External beam radiation therapy alone

The most recently published multicentre prospective randomised trial carried out by the PORTEC study group aimed to find out whether AP-EBRT improves loco-regional control and survival in patients with Stage I endometrial carcinoma [17]. After total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), without lymphadenectomy, 715 patients were randomised to 46 Gy pelvic radiotherapy or no further treatment. Based on their results an altered risk group classification emerged in contrast to the GOG one. They identified two risk groups as histological grades 1 and 2 which were grouped together because of the small difference found between their prognostic significance. Patients belong to a *low-risk* group if they are younger than 60 and have superficially invasive grade 2 tumours. The risk of loco-regional relapse without radiotherapy in this group was 5% or less. On the other hand patients over 60 with deeply invasive grade 1 and grade 2 tumours or superficially invasive grade 3 tumours belong to the *high-risk* group. The loco-regional relapse rate was 5% in the radiotherapy group and 18% in the control group. From the PORTEC trial it can be concluded that AP-EBRT clearly reduces the risk for pelvic recurrences but does not improve the survival rate of patients with high-risk features [17]. Despite identifying a high-risk group of patients, the authors of the trial do not unambiguously recommend AP-EBRT, as the reduction of pelvic recurrences may not be sufficient to counterbalance the treatment morbidity.

A similar randomised study was accomplished by the GOG (GOG #99) but this time surgical staging with pelvic and para-aortic lymph node sampling was performed [18]. After TAH, BSO and lymph node sampling a number of 390 eligible patients were randomised to receive 50.4 Gy to the pelvis or no further treatment. The study predominantly included intermediate-risk patients: 60% were in Stage IB, 30% in Stage IC and 80% had grade 1 and grade 2 tumours. Although the data are not mature in this trial either, according to a preliminary report 17 patients have failed in the pelvis or vagina in the observation arm (8.5%) in comparison to three (two of these did not receive their randomised treatment) in the irradiation arm (1.6%). The estimated 2-year progression-free interval rate was 88% in the observational arm vs 96% in the radiation arm. Most of the patients in the observation arm failed in the vagina alone: 13 out of 17 patients with loco-regional relapses. Both the GOG and the PORTEC study demonstrated that most of the recurrences were located in the vagina (73%), mainly in the vaginal vault. An obvious question arises from this finding: could VBT in the control group have prevented most of the recurrences?

Table 1. — *Clinical results of adjuvant brachytherapy.*

| Author | Study | No. of patients | Risk factors | LAD | Adjuvant XRT | Therapy BT | Recurrence patterns |
|---|---|---|---|---|---|---|---|
| Mohan *et al.* [5] | R | 192/159 | 6% G3 17% IC<br>3% adenosq.<br>3% papillary<br>1% clear | 100% extended PLN & ALN | No | HDR | Neither V nor P<br>6 D; 1 U |
| Fanning [11] | P | 265/66 | 66 pts were at intermediate-risk:<br>52% G3<br>27% IC<br>11% IIA<br>23% IIB | 100% Extended | No | 22 HDR<br>44 LDR | Neither V nor P 2 D |
| Anderson *et al.* [21] | R | 102/102 | 15% G3<br>28% IC<br>5% clear cell & papillary- serous | 15% sampling PLN<br>45% sampling PLN & ALN | No | HDR | 1 VC; 2 P; 4 D |
| Ng *et al.* [22] | R | 489/77 | 77 pts were at high-risk:<br>44% G3<br>78% IC | 100% extended PLN & ALN | No | LDR | 7 V (5/7 of vaginal recurrences were in the middle or lower 1/3 of the vagina, outside the treatment field)<br>1 P; 3 D |
| Alektiar *et al.* [24] | R | 233/233 | No | 9% sampling PLN & ALN | No | HDR | 3 V; 2 P; 2 P+D<br>3 D |
| Eltabbakh *et al.* [25] | P | 332/332 | 8.7% m.p.c.<br>2% papillary<br>2% adenosq.<br>1% other cytology | 11.5% sampling PLN & ALN | No | LDR | 6 pts had 12 sites of recurrence (median 2 sites/pt.):<br>2 P; 1 IN; 9 D |

Note: the overwhelming majority of these studies' patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy.
N/n: number of patients in the study group/total number of patients evaluated; LAD: lymphadenectomy; XRT: external radiotherapy; BT: brachytherapy; R: retrospective; P: prospective; PLN: pelvic lymphadenectomy; ALN: aortic lymphadenectomy; HDR: high dose rate; LDR: low dose rate; V: vaginal; VC: vaginal cuff; P: pelvic; D: distant; U: unknown; G: grade; m.p.c.: malignant peritoneal cytology; pts.: patients; adenosq: adenosquamous.

## 2. Brachytherapy alone

There is one old randomised trial that tested adjuvant low-dose-rate BT (LDR-BT) vs the combination of AP-EBRT and LDR-BT [19]. This trial could demonstrate a minor, statistically not significant advantage in terms of loco-regional control of the combined modality over LDR-BT applications, but no survival benefit. Furthermore morbidity issues were not at all mentioned in this trial. There are no randomised studies to indicate which patients may be appropriate to treat with VBT alone. Most of the studies involving VBT are retrospective or non-randomised with an imbalance of surgical-pathological risk factors between different patient subgroups.

The rate of vaginal failures after surgery alone is reported as 3% to 15% in most retrospective series [20]. The most common site of vaginal recurrences is in the region of the hysterectomy scar in the apical vagina. Due to this rate of vaginal failures and the low risk of complications associated with vaginal treatment, it is appropriate to consider vaginal vault irradiation alone in **surgically staged** patients who have had *intermediate-risk* Stage I disease. The results of a good number of clinical studies support this therapeutic strategy (Table 1). There is also evidence from several studies [11, 21-22] that even patients with *high-risk* Stage I disease are adequately treated with surgical staging and vaginal cuff irradiation. The opinion of the authors of these studies is that in the absence of pelvic node involvement postoperative vaginal cuff irradiation reduces local recurrence and has a therapeutic ratio superior to pelvic irradiation in patients at risk for isolated cuff recurrences [5, 21, 23].

A similar excellent outcome may be achieved **without lymphadenectomy** as reported by Alektiar *et al.* and Eltabbakh *et al.* [24, 25] however none or few patients were at high-risk in their study populations.

## Conclusion

From the studies presented above it can be concluded that: no adjuvant therapy is recommended in patients with *low risk* Stage IA grade 1 and grade 2 tumours [20]. For Stage IB, grade 1 and grade 2 patients after sur-

gery without pelvic lymph node dissection postoperative vaginal BT alone is sufficient, as is the case for patients in Stage IA grade 3 and Stages IB-IC who underwent pelvic lymph node dissection [11, 14, 20]. Without pelvic lymph node dissection, AP-EBRT alone seems to be indicated for Stage IB grade 3 and IC all grades of disease because the risk of loco-regional recurrence after surgery alone without pelvic lymphadenectomy is higher than 10% [17]. Based on these findings it seems that pelvic irradiation is unjustified for most of the Stage I endometrial carcinoma cases. What would be necessary to find out is the effectiveness of VBT alone compared to AP-EBRT alone in the high-risk group of patients without lymph nodal dissection [26, 27].

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