Stage IB Endometrial Cancer

Does Lymphadenectomy Replace Adjuvant Radiotherapy?

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Background: The role of surgical lymph node dissection and adjuvant radiation therapy (RT) in early stage endometrial cancer is no longer clearly defined. The increased appreciation of lymphadenectomy and the absence of survival advantage from adjuvant RT rise controversies how patients should adequately be treated in stage IB endometrial cancer. The aim of this review is to rule out the validity of either treatment option and determine which preference provides the best therapeutic benefit.
Methods: Reports of relevant studies obtained from a search of PubMed and studies referenced in those reports were reviewed.
Results: Based on the available data in the literature, for stage IB grade 1 or 2, the risk of pelvic relapse is considered too low to justify pelvic RT. However, intravaginal RT (IVRT) should be recommended for those $\geq$ 60 years old or with lymphovascular invasion (LVI). For patients with stage IB grade 3 (and IC all grades), the treatment recommendation is mainly based on whether surgical lymph node staging was performed. These patients have – without surgical lymph node staging – a high risk of pelvic recurrence and should therefore primarily undergo relaparotomy for lymphadenectomy or pelvic RT as second choice. If these patients had a surgical lymph node staging, then IVRT alone is a reasonable alternative to pelvic RT.
Conclusion: Overall survival may not be the only ideal endpoint for stage IB endometrial cancer since causes of death are mostly other than endometrial cancer. Conventional pelvic RT may be overtreatment in some patients, in particular in those patients with a large number of negative lymph nodes after lymphadenectomy. However, negative surgical staging should not be understood as adjuvant RT can be omitted in all patients.

Key Words: Early stage endometrial cancer · Radiotherapy · Side effects · Local recurrence · Survival

Strahlenther Onkol 2007;183:600–4
DOI 10.1007/s00066-007-1801-3

Endometriumkarzinom im Stadium IB. Kann die Lymphonodektomie adjuvante Strahlentherapie ersetzen?

Hintergrund: Unklarheit besteht bezüglich des Stellenwertes des operativen Lymphknotenstagings sowie der adjuvanten Strahlentherapie beim frühen Endometriumkarzinom. Der zunehmende Einsatz der pelvinen und paraaortalen Lymphonodektomie und der nicht nachweisbare Überlebensvorteil durch die adjuvante Strahlentherapie nähren die Diskussion darüber, wie Patientinnen mit einem Endometriumkarzinom im Stadium IB korrekterweise behandelt werden sollten. Das Ziel dieser Übersicht ist es, den Stellenwert einer jeden Therapieoption zu überprüfen und ihren jeweiligen Indikationsbereich zu bestimmen.
Methodik: Als Grundlage für diese Übersicht dienten in MEDLINE veröffentlichte Untersuchungen sowie darin zitierte Studien.
Ergebnisse: Basierend auf verfügbaren Daten ist das Risiko für ein pelvines Rezidiv nach einem Endometriumkarzinom im Stadium IB G1 und 2 als so gering einzustufen, dass eine Beckenbestrahlung generell nicht zu rechtfertigen ist. Dennoch sollten Patientinnen $\geq$ 60 Jahre und solche mit einer Lymphangioinvasion eine Radiatio des Scheidenstumpfes im Sinne einer vaginalen Einlage erhalten. Im Stadium IB G3 sollte die pelvine und paraaortale Lymphonodektomie durchgeführt werden. Hier stellt die Beckenbestrahlung als alternative Therapieoption zur Lymphonodektomie lediglich die zweite Wahl dar.
Schlussfolgerung: Nachdem die meisten Patientinnen mit einem Endometriumkarzinom im Stadium IB eher an ihren Begleiterkrankungen als an ihrem Tumorleiden versterben, erscheint das Gesamtüberleben als alleiniges Entscheidungskriterium für oder wider eine adjuvante Strahlentherapie nicht als der ideale Endpunkt. Sicherlich stellt die adjuvante Beckenbestrahlung bei vielen Patientinnen eine Übertherapie dar; dennoch darf der prognostische Wert eines unauffälligen Lymphknotenstagings nicht dahingehend überinterpretiert werden, bei allen Patientinnen auf eine adjuvante Strahlentherapie verzichten zu können.

Schlüsselwörter: Frühes Endometriumkarzinom · Strahlentherapie · Gesamtüberleben · Lokale Tumorkontrolle

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Received: August 14, 2007; accepted: September 3, 2007

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries. As the majority of patients represent with early-stage disease, the overall prognosis of endometrial cancer patients is favorable. However, adequate adjuvant therapy in stage I, particular in stage IB cancer, remains under discussion since recent published studies have revealed 5-year overall survival rates up to 90% for patients who were treated with total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) alone, without adjuvant radiation therapy (RT) [1, 11, 12, 17, 19] although tremendous effort has been done for further improvement in brachytherapy techniques in different tumor entities to lower radiation associated side effects [15, 27, 31, 37].

Endometrial cancer primarily is a disease of postmenopausal women, with significant concurrent morbidities such as obesity, diabetes mellitus, and hypertension. Although comorbidity data in the Gynecologic Oncology Group (GOG) randomized trial of surgery with or without adjuvant radiotherapy (GOG 99) as treatment for early stage endometrial cancer were not collected in the protocol [19], a recent prospective study reported that 68% of women with early endometrial cancer are obese [36]. It is well known from other cancer entities that comorbidities like obesity may significantly effect overall recurrence rates, and other clinical outcomes as well as treatment complications [5, 7, 21]. Therefore, taking the good prognosis for most patients into account, the challenge is to effectively identify those patients who might have an objective benefit from further adjuvant radiation therapy while avoiding overtreatment of cases in which therapeutic side effects might unnecessarily outweigh potential benefit from adjuvant therapy.

However, the problem we face in clinical practice is what should we further recommend a patient with an early stage endometrial cancer stage IB who has been already surgically treated with a TAH and BSO:

(1) Secondary pelvic with or without aortic lymphadenectomy and
(2) adjuvant radiation therapy or
(3) radiation therapy alone?

Lymphadenectomy in Stage IB Endometrial Cancer

Since the GOG 33 staging study [10, 21], which demonstrated an overall risk of 9% of pelvic lymph node metastases in clinical stage IB endometrial cancer, it has been suggested even intermediate- and low-risk endometrial cancer patients have to undergo standard lymphadenectomy. At this point, however, it has to be noted, that only 12% of patients in that study where found to have macroscopic extrauterine disease. Of these, 51% had pelvic and 23% aortic lymph node metastases. Among the patients without macroscopic spread in the peritoneal cavity, only 7% had positive pelvic and 4% positive aortic lymph nodes. Patients with grade 3 diseases were at high risk, namely more than 10%, to have lymph node metastases, while all other cases were at low or moderate risk [24]. These data are consistent with the COSA-NZ-UK trial, which demonstrates the same risk for positive nodes of 7% (COSA-NZ-UK 1996). However, the question remains, in which clinical situation completion of lymphadenectomy should be advocated in stage IB endometrial cancer. Concluding the results from GOG 33 and the COSA-NZ-UK trial all patients at high risk should have lymph node dissection. Those are patients with adenosquamous, serous or clear-cell carcinomas and grade 3 tumors of any histological type.

Another important question remains the number of lymph nodes which have to be removed. Should a standard been set to the number of lymph nodes that should be dissected? Although several retrospective studies reported improved outcome in patients after lymphadenectomy, those studies had selection bias and stage migrations [14, 23]. Nevertheless, the number of removed lymph nodes remains between 7 and 11 [20, 35]. In a recently published analysis of 509 patients the number of 11 removed nodes has been defined that at least has to be dissected to improve overall survival (hazard ratio [HR] 0.25, $p < 0.0001$) only in patients with adenosquamous, serous or clear-cell carcinomas or grade 3 tumors [9]. However, taking data from all trials together no survival benefit was found between 6.363 women with no and 2.821 with lymphadenectomy, in those patients with stage IB grade 1 and 2 endometrial carcinomas. This question incorporates the controversy whether lymphadenectomy has either diagnostic or even therapeutic importance. Furthermore, if lymph node dissection is therapeutic, can adjuvant RT be omitted for all node-negative patients including those with grade 3 tumors? Obviously not, since the only randomized trial [19] facing that question revealed a 27% relapse rate without RT.

The concern of lymph node dissection includes the prolongation of operation time with potential short-term and long-term side effects.

Taking all these findings together, lymphadenectomy in stage IB endometrial carcinoma should only be performed in patients with adenosquamous, serous or clear-cell carcinomas and grade 3 tumors of any histological type.

Adjuvant RT in Stage IB Endometrial Cancer

Up until the beginning of the 1990s, the adjuvant treatment for early stage endometrial cancer was clearly defined. Most patients with less than half myometrial invasion and with grade 1 or 2 histology received intravaginal brachytherapy (IVBT), whereas those with deep invasion or grade 3 received pelvic RT. Nevertheless, two recent developments have questioned the adjuvant RT in early endometrial cancer. First, the increased use of lymphadenectomy has called into question the validity of using postoperative pelvic RT for patients with pathologically negative lymph nodes [21, 23, 34]. Second, the results of some prospective randomized trials reported no survival advantage with the addition of pelvic RT.

In 1980, Aalders et al. have published the results of a first randomized study. 540 patients with stage I endometrial can-

cer were randomized after TAH and IVBT to additional pelvic RT or observation [1]. Although pelvic RT reduced vaginal and pelvic recurrence (1.9% vs. 6.9%, $p < 0.01$), more distant metastasis was found in the pelvic RT group (9.9% vs. 5.4%), and survival was not improved. Only the subgroup with grade-3 tumors with deep (≥ 50%) invasion showed both improved local control and survival after additional pelvic RT.

The Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) trial randomized 715 patients with stage IB (grades 2 and 3) and with IC (grades 1 and 2) after TAH-BSO to observation or pelvic RT with 46 Gy [12]. No lymph node sampling was performed. At 5 years, there was a significant difference in the rates of vaginal/pelvic recurrence in favour of adjuvant pelvic RT (4% vs. 14%, $p < 0.001$). Overall survival, however, was not different between the two groups.

Scholten et al. showed in an update of PORTEC that age ≥ 60 years was an independent predictor of locoregional relapse (HR 3.4; $p = 0.0005$) [32]. Furthermore, for patients ≥ 60 years with either grade 3 histology or ≥ 50% myometrial invasion, the 10-year risk of locoregional relapse (most were vaginal) increased from 4.6% for those treated with adjuvant RT to 23.1% for those treated with surgery alone.

The third randomized trial was GOG 99. 448 patients with stage IB–IIB (grades 1–3) disease who all underwent TAH-BSO and, different from the PORTEC trial, bilateral pelvic and para-aortic lymphadenectomy, were randomized to observation versus pelvic RT to a total dose of 50.4 Gy [19]. At 2 years, significant difference in the rates of relapse in favor of the adjuvant pelvic RT arm (3% vs. 12%, $p = 0.007$) was shown. There was, however, no significant difference in 4-year overall survival.

Based on these data, pelvic RT is recommended nowadays for patients after TAH-BSO without lymphadenectomy and with additional risk factors (age > 60 years, deep myometrial invasion, presence of lymphovascular space invasion, adenosquamous, serous or clear-cell carcinomas and grade 3 tumors of any histological type).

The PORTEC and GOG 99 were set out to determinate if adjuvant pelvic RT is needed in early-stage endometrial cancer, but neither was large enough to answer the question of overall survival. Both trials, however, showed statistically significant differences in terms of relapse.

However, the rate of vaginal relapse is not the same for all early-stage endometrial cancer. In the surgery alone arm of the PORTEC trial, the risk of vaginal relapse at 5 years was 5% for stage IB grade 2, 14% for stage IB grade 3, 10–13% for stage IC grade 1–2 [2].

Mariani and coworkers reported on 632 patients with stage I endometrial cancer, of whom 508 were treated with surgery alone. The 5-year rate of vaginal relapse was 2% for those with grade 1 or 2 compared with 11% for those with grade 3 ($p < 0.0001$) [22].

There has never been a randomized trial comparing IVBT alone to pelvic alone, but most data in the literature on high-dose rate (HDR)-IVBT show a rate of vaginal recurrence similar to that with pelvic RT (0–2%) and a very favorable rate (0–1%) of significant late sequences [4, 6, 18, 28, 33].

Table 1. Results of intravaginal radiotherapy alone for IB Grade 1 or 2.

Tabelle 1. Ergebnisse einer alleinigen intravaginalen Brachytherapie im Stadium IB G1 und 2.

Author	Year	Patients (n)	Pelvic recurrence (%)
Alektiar et al. [3]	2002	233	2
Anderson et al. [6]	2000	62	2
Petereit et al. [28]	1999	153	1

Table 2. Pelvic relapse after intravaginal radiotherapy alone and lymph node sampling for IB Grade 3 and IC.

Tabelle 2. Pelvine Lokalrezidivrate nach alleiniger intravaginaler Brachytherapie und Lymphonodektomie für Stadium IB G3 und IC.

Author	Year	Patients (n)	n (%)
Anderson et al. [6]	2000	44	1 (2,2)
Horowitz et al. [16]	2002	81	2 (2,4)
Solhjem et al. [33]	2005	60	0 (0)

Pelvic recurrence when using IVRT alone is a function of tumor stage/grade and whether surgical lymph node staging was performed. For patients with stage IB grade 1 or 2, the risk of pelvic recurrence ranges from 0–2% [3, 6, 28] (Table 1). Stage IB grade 3 and IC patients are considered at high risk for having positive pelvic lymph nodes; therefore, whether or not surgical lymph nodes staging was performed is important. In Aadler's randomized trial of IVRT alone versus pelvic RT + IVRT, those with IB grade 3 and stage IC without lymph nodes staging had a higher rate of locoregional relapse when treated with IVRT alone, indicating that in the absence of surgical staging those patients need pelvic RT. For stage IB grade 3 and IC with surgical lymph node staging, IVRT alone seems to provide low-enough pelvic recurrence (range 0–2.4%) to justify omitting pelvic RT [6, 16, 33] (Table 2).

Intravaginal RT is a reasonable alternative to conventional pelvic RT in most patients with early endometrial cancer, especially for those who had surgical lymph node staging. There are some patients, however, who are not good candidates for surgical staging or with poor prognostic factors in whom pelvic RT is generally recommended. The former include obese patients or those with other morbidity that precludes comprehensive surgical staging.

Complications of Pelvic RT

The 5-year actuarial rates of late sequences (grade 1–4) in the PORTEC trial were 26% for the RT arm compared with 4% in the surgery-alone arm ($p < 0.0001$). However, when grade 1 toxicity (68% of all late sequences) was excluded, the corresponding rates dropped to 17% and 4%, respectively. Furthermore, the rates of grade 3–4 sequences was only 3%

in the RT group [13]. All these grade 3–4 sequences were of the gastrointestinal tract.

If extensive surgery must be combined with RT or a systemic therapy there is a significant increased morbidity [8]. In GOG 99 [19], the simple 4-year incidence of grade 3 gastrointestinal sequences was 8% in the RT arm.

Multiple variables were evaluated in another study as potential reasons for these side effects, but neither stage, hypertension, diabetes mellitus, nor prior pelvic surgery, but only older age (> 65 years), lymphadenectomy, the use of a brachytherapeutic vaginal boost, and the volume of pelvic tissue irradiated was the variable that approached statistical significance [8].

Pelvic Intensity-Modulated Radiation Therapy (IMRT)

There have been several publications on the dosimetric advantages of pelvic IMRT [29, 30], but more importantly there are data to show that the morbidity could be decreased with IMRT. Mundt et al. reported on 36 patients with gynecologic cancers treated with pelvic IMRT compared with 30 patients treated with conventional pelvic RT [25]. Median follow-up in the IMRT and the conventional RT groups were 19.6 and 30.2 months, respectively. Overall, IMRT patients had a lower rate of chronic gastrointestinal toxicity (11.1% vs. 50%, $p = 0.001$) than patients with conventional pelvic RT. The percentage of IMRT patients with grade 1, 2, and 3 toxicity were 8.3%, 2.8%, and 0%, respectively. Corresponding percentages in the conventional RT group were 30%, 16.7%, and 3.3%. However, longer follow-up and more patients are clearly needed to ascertain whether the benefits of IMRT treatment seen here translate into true long-term reductions in late side effects.

Conclusion

Based on the available data in the literature, for stage IB grade 1 or 2 the risk of pelvic relapse is considered too low to justify pelvic RT. Therefore, the treatment recommendation is based on the risk of vaginal relapse, which seems to be related to the patient's age and LVI. We recommend IVRT for those ≥ 60 years old or with LVI. For patients with stage IB grade 3 (and IC all grades), the treatment recommendation is mainly based on whether surgical lymph node staging was performed. These patients have – without surgical lymph node staging – a high risk of pelvic recurrence and should be treated with pelvic RT. Whether IVRT should be added to pelvic RT has been a topic of extensive debates. If these patients had a surgical lymph node staging, then IVRT alone is a reasonable alternative to pelvic RT.

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