Overview

Adjuvant Chemotherapy in Endometrial Carcinoma: Overview of Randomised Trials

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ABSTRACT:
Endometrial cancer generally has a good prognosis because most cases are diagnosed in stage I. It is possible to identify subgroups of patients with early stage endometrial cancer with a poor prognosis. Despite a traditional generous use of adjuvant radiotherapy those patients have less than an 80% 5-year overall survival. In this group there is a need for an effective systemic adjuvant therapy. Two randomised studies have shown better response rates but no significant difference in overall survival for doxorubicin–cisplatin vs doxorubicin in advanced or recurrent endometrial cancer. Mainly on the basis of the superior response rates, doxorubicin–cisplatin was for many years regarded as the standard chemotherapy in endometrial cancer. GOG-177 was the first phase III study on chemotherapy in advanced or recurrent endometrial cancer that showed a survival advantage. Paclitaxel–doxorubicin–cisplatin was better than doxorubicin–cisplatin, but the toxicity of the three-drug regimen has precluded general acceptance. Paclitaxel–carboplatin has rendered high response rates in endometrial cancer and is widely used, despite the lack of evidence based on randomised studies. GOG-122 was a pivotal randomised study that compared doxorubicin–cisplatin with whole abdominal radiotherapy in advanced optimally operated endometrial cancer and showed that chemotherapy with doxorubicin–cisplatin resulted in superior survival. Two recent studies have compared adjuvant chemotherapy (cyclophosphamide–doxorubicin–cisplatin) with adjuvant radiotherapy in early stage endometrial cancer. Both studies failed to show a difference between the treatments, but neither was powered to show non-inferiority. Another study (NSGO-EC-9501/EORTC-55991) compared adjuvant radiotherapy plus chemotherapy with adjuvant radiotherapy and showed better survival with the combination. The implications of these studies are discussed.


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Key words: Adjuvant, chemotherapy, endometrial, micrometastic

Statement of Search Strategies Used and Sources of Information

A search was carried out in PubMed using the following search terms: 'endometrial neoplasms' and 'adjuvant chemotherapy' and 'randomised'. An extended search in PubMed was also carried out with the search strategy outlined in the Cochrane protocol 'Adjuvant chemotherapy for endometrial cancer'.

Introduction

Endometrial cancer is the most common gynaecological cancer in the Western world. It was estimated that worldwide around 200 000 women were diagnosed with endometrial cancer in 2002 [1]. In Sweden the incidence has increased by 47% from 19 cases per 100 000 women-years in 1960 to 28 cases in 2006 (age standardised to the Swedish population in 2000) [2]. Endometrial cancer generally has a good prognosis because around 80% are diagnosed in stage I. However, stage for stage, the prognosis is about the same as for ovarian cancer [3]. Although generally the prognosis for early stage endometrial cancer is excellent, there are subgroups with a high risk for micrometastatic disease, e.g. International Federation of Gynecology and Obstetrics (FIGO) stage IC grade 3 with 79% 5-year overall survival [3], despite that most of these patients have been treated with adjuvant radiotherapy. In those high-risk patients there is a need for systemic adjuvant therapy.

Endometrial cancer has traditionally been thought to be a rather chemotherapy insensitive tumour, but gradually this view has changed. This is an overview of the randomised studies carried out on adjuvant chemotherapy in endometrial cancer.

Chemotherapy in Advanced or Recurrent Endometrial Cancer

Phase II studies on chemotherapy in advanced or recurrent endometrial cancer have shown response rates exceeding...
20% mainly with anthracyclines, platinum compounds, and taxanes [4]. Two large randomised studies (EORTC 55872 and GOG-107) have compared doxorubicin and cisplatin (AP) with doxorubicin [5,6]. Both studies found that the combination gave better response rates, but no significant differences in survival. Mainly on the basis of the superior response rates, the combination of doxorubicin and cisplatin was for many years regarded as the standard in endometrial cancer. In GOG-177, the Gynecologic Oncology Group (GOG) compared a taxane combination (paclitaxel, doxorubicin, cisplatin; TAP) with AP in 273 (263 eligible) chemotherapy-naive women with measurable FIGO stage III–IV, or recurrent endometrial carcinoma of any cell type [7]. Both response rates, overall survival and progression-free survival (PFS), were significantly better with TAP. However, the TAP combination was toxic, with 39% grade 2–3 peripheral neurotoxicity compared with 5% in patients receiving AP. All patients in the TAP arm received a granulocyte stimulator (filgrastim). The imbalance in the number of deaths to which treatment may have contributed (five on TAP vs none on AP) is of note. However, only two of the five deaths (neutropenic fever and acute myelogenous leukemia) on TAP were, according to the investigators, clearly treatment related. The toxicity of this regimen may have precluded its use in many centres.

Paclitaxel–carboplatin (TcP) is a commonly used drug combination in gynaecological cancer. Apart from its neurotoxicity it is a well-tolerated and rather atoxic regimen. Phase II studies in advanced or recurrent endometrial cancer have shown response rates in the range of 60–70% [4,8]. The GOG is presently running a randomised study (GOG-209) comparing TcP with TAP with the goal of randomising 900 patients [9]. It will, however, take some years before we know the results from that study. Meanwhile, despite the lack of evidence based on randomised studies, some chose to use the TcP combination.

**GOG-122**

The pivotal study [10] that changed the way many looked at endometrial cancer and chemotherapy was GOG-122. Four hundred and twenty-two (396 evaluable) patients with FIGO stage III or IV endometrial carcinoma of any histology who were entered into this randomised trial, which compared chemotherapy with whole abdominal radiotherapy (WAR). Eligibility required total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), surgical staging, tumour resection, and no single site of residual tumour greater than 2 cm. Nodal sampling was optional. Patients with positive para-aortic lymph nodes were required to have negative scalene node biopsies and chest computed tomography. WAR was given with 30 Gy in 20 fractions, with an additional 15 Gy pelvic boost. Chemotherapy consisted of doxorubicin (60 mg/m²) and cisplatin (50 mg/m²) every 3 weeks for seven cycles, followed by one cycle of cisplatin.

Both overall survival and PFS were significantly better for patients in the chemotherapy arm. The treatment effect was comparable in subgroup analyses according to stage, substage, age, cell type, and residual disease status. Grade 3 and 4 adverse effects (particularly haematological, gastrointestinal, cardiac, and neurological) were significantly more common in the AP arm. Treatment may have contributed to the death of five patients in the WAR arm and eight patients in the AP arm. The investigators recommended the use of haematopoietic growth factors to minimise complications associated with neutropenia in selected high-risk patients, and that patients receiving more than 300 mg/m² doxorubicin should be closely monitored for left ventricular function. Less than two-thirds of patients completed all eight cycles of chemotherapy as prescribed.

There has been a lively discussion on whether patients with serous or clear cell carcinomas should participate in the same studies as patients with endometrial carcinomas. The GOG has analysed their chemotherapy studies in endometrial cancer [11]. They found no evidence that serous/clear cell carcinomas responded differently to chemotherapy than endometrioid carcinomas and, hence, the GOG will continue to include serous/clear cell carcinomas in their chemotherapy studies.

**Randomised Studies on Adjuvant Chemotherapy in Early Endometrial Cancer**

**GOG-34**

The first randomised study (GOG-34) on adjuvant chemotherapy in endometrial cancer was initiated by the GOG [12]. Between 1977 and 1986 they randomised 224 (181 evaluable) patients with endometrial carcinoma FIGO stage I and II (occult), all histological grades with one or more of the following high-risk features: (1) ≥ 50% myometrial invasion, (2) histologically documented pelvic or para-aortic metastases, (3) cervical extension without clinical evidence of cervical engagement (occult), or (4) adnexal metastases. All patients underwent TAH-BSO, selective pelvic and para-aortic lymph node dissection, and peritoneal cytology. After surgery, patients received 50 Gy adjuvant pelvic external radiotherapy (XRT). A para-aortic field was added if para-aortic node metastases were documented. Patients were randomised to observation or to receive doxorubicin 45 mg/m² after the completion of XRT. The maximum cumulative dose of doxorubicin was 400 mg/m² (in the later part of the study 500 mg/m²).

The study was terminated prematurely because of slow recruitment. Twenty-seven per cent of patients randomised to doxorubicin did not receive doxorubicin and 2% only received one course, usually due to patient refusal. No significant difference in overall survival or PFS could be seen between the treatment arms. The investigators concluded that the study was unable to determine what effect doxorubicin had on recurrence because of protocol violations, the small sample size, and the number of patients lost to follow-up.

**Italian Study**

Between 1990 and 1997, an Italian study [13] randomised 345 (340 evaluable) patients with histologically confirmed...
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endometrioid, adenoacanthoma or adenosquamous carcinoma and FIGO stage IC grade 3, or stage IIA–B grade 3 with \( \geq 50\% \) myometrial invasion or FIGO stage III disease. To rule out FIGO stage IV disease, all patients underwent chest radiography and abdominal–pelvic ultrasound. All patients underwent primary surgery consisting of TAH-BSO, with or without excision of the vaginal cuff/upper third of the vagina, and selective pelvic and para-aortic node sampling. Vaginal hysterectomy or radical hysterectomy were also allowed.

The patients were randomised to either adjuvant chemotherapy \((n = 174)\) with cyclophosphamide \((600 \text{ mg/m}^2)\), doxorubicin \((45 \text{ mg/m}^2)\) and cisplatin \((50 \text{ mg/m}^2; \text{CAP})\) given every 4 weeks for five cycles or adjuvant pelvic XRT \((n = 166)\); 45–50 Gy in 5–7 weeks. Patients who had lymph node involvement received additional para-aortic lymph node irradiation.

During follow-up the patients were evaluated with periodic visits every 3 months in the first 3 years, every 6 months in the next 2 years, then annually. At each follow-up, symptoms were recorded, and abdominal palpation and a pelvic examination were carried out. Vault smears were taken every 6 months for the first 2 years, then annually. Chest radiograms were taken once a year.

Of the patients assigned XRT, 88\% completed treatment as planned. Two per cent stopped treatment because of toxicity and 6\% declined treatment. Among patients assigned to chemotherapy, 75\% received five treatment cycles as planned and 89\% received at least one cycle and were assessable for toxicity. The main reason for not giving all five cycles was excessive bone marrow toxicity. Seven per cent declined adjuvant chemotherapy.

Major late toxic effects in patients who received XRT were gastrointestinal, including 3\% bowel obstruction with three of these five patients requiring surgical intervention, 4\% grade 3 radiation proctitis, and 16\% grade 3 diarrhoea. Urinary tract complications (severe actinic cystitis) were recorded in 5\%. The toxicity of CAP was mainly myelotoxicity; 31\% grade 3 and 5\% grade 4 neutropenia, 34\% grade 2–3 anaemia, and 6\% grade 2–3 thrombocytopenia. The incidence of nausea and vomiting was relatively low; 10\% grade 3 and for one patient grade 4. Other serious toxicities (grade 3) occurred in \(< 3\%\) of the patients randomised to chemotherapy. There were no treatment-related deaths.

At the median follow-up time of 96 months, 60 recurrences and nine deaths (together 38\%) had occurred as a first event in patients on XRT, and 56 recurrences and 10 deaths (together 42\%) as a first event in the patients on chemotherapy. The overall number of observed deaths was 36\% in the XRT arm and 34\% in the chemotherapy arm. A comparison of the Kaplan–Meier curves for PFS and overall survival rendered non-significant hazard ratios of 0.95 (confidence interval 0.66–1.36; \( P = 0.78 \)) and 0.88 (confidence interval 0.63–1.23; \( P = 0.45 \)), respectively. The 5-year PFS for the patients on chemotherapy was 63\% (confidence interval 55–70\%) vs 63\% (confidence interval 55–70\%) for patients on XRT, whereas the 5-year overall survival was 66\% (confidence interval 59–73\%) compared with 69\% (confidence interval 61–76\%), respectively.

Multivariate analysis confirmed that there was no real difference between chemotherapy and XRT regarding PFS and overall survival.

Among patients randomised to XRT, the initial site of recurrence was distant (extra-abdominal or liver) in 21\%, local in 7\%, concurrent distant and local in 5\%, and of unknown type in 3\%, whereas for the patients randomised to chemotherapy, the initial site of recurrence was distant in 16\%, local in 11\%, concurrent local and distant in 5\%, and of unknown type in 1\%. Their study was not powered to detect clinically significant differences in the incidence of relapses.

The investigators concluded that the trial failed to show an improvement in PFS or overall survival in patients treated with adjuvant chemotherapy or XRT, that both therapeutic approaches were associated with acceptable toxicities, and that the distribution of local and distant relapses in the respective randomisation arms suggests that XRT might achieve better locoregional control, whereas systemic chemotherapy might control distant metastases better. This made the investigators speculate if the combination of concurrent or sequential adjuvant radio- and chemotherapy could further improve the results.

**JGOG-2033**

A study from the Japanese Gynecologic Oncology Group (JGOG) \([14]\) randomised 475 (385 eligible) patients between 1994 and 2000 (JGOG-2033). The inclusion criteria were FIGO stage IC–IIIC endometrial carcinoma with \( \geq 50\% \) myometrial invasion. Patients were required to be under 75 years old and to have undergone an initial surgery, including TAH-BSO with no residual tumour. Pelvic lymphadenectomy was carried out in 96\% of the patients, and para-aortic lymphadenectomy in 29\%.

Patients in the control arm received pelvic XRT with antero-posterior fields, 45–50 Gy within 4–6 weeks. Para-aortic irradiation was added in 6\% with para-aortic metastases and 3\% received brachytherapy. The chemotherapy group received CAP: cyclophosphamide 333 mg/m\(^2\), doxorubicin 40 mg/m\(^2\), and cisplatin 50 mg/m\(^2\) every 4 weeks for three or more courses.

The study was powered to detect a difference in overall survival rate at 5 years of 13\% from 67 to 80\% with a significance level of 5\% and a power level of 80\%. The required sample size was estimated to be 173 for each group.

The follow-up scheme was not described. The median follow-up period was 60 months. The compliance to treatment was extremely good. Treatment was completed in 99\% (184/186) and 97\% (183/188) of the patients in the XRT and chemotherapy groups, respectively.

Grade 3–4 toxicities were experienced in 2\% of the XRT group and in 5\% of the chemotherapy group. Bowel obstructions were the main complication in the XRT group, and myelosuppression in the chemotherapy group. No treatment-related deaths occurred in either group.

The progression rate was 16\% in the XRT group and 17\% in the chemotherapy group. The patterns of progression were similar in both treatment groups. Specifically, the rate of
intrapelvic progression sites, such as the pelvis or vagina, was 7% in both the XRT and chemotherapy groups.

The 5-year PFS was 84% in the XRT group and 82% in the chemotherapy group (hazard ratio 1.07, confidence interval 0.65–1.76; \( P = 0.726 \) ) and the 5-year overall survival was 85% in the XRT group and 87% in the chemotherapy group (hazard ratio 0.72, confidence interval 0.40–1.29; \( P = 0.268 \)). Three subgroup analyses were described. In the low- to intermediate-risk subgroup (stage IC patients under 70 years of age and with grade 1–2 endometrioid adenocarcinoma, \( n = 190 \)), the 5-year PFS in the XRT and chemotherapy groups were 95 and 88%, respectively (\( P = 0.110 \)), and 5-year overall survival 95 and 91%, respectively (\( P = 0.281 \)). A high- to intermediate-risk group was defined as (1) stage IC patients over age 70 years or having grade 3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology). According to the inclusion criteria, all patients had \( \geq 50\% \) myometrial invasion. Among these 120 patients, the PFS rate was 84% vs 66% (hazard ratio 0.44, confidence interval 0.20–0.97; \( P = 0.024 \)) and the overall survival rate 90% vs 74% (hazard ratio 0.24, confidence interval 0.09–0.69; \( P = 0.006 \)) favouring chemotherapy. The high-risk group consisted of stage IIIA patients with factors other than a positive peritoneal cytology and stage IIB and IIIC patients; \( n = 75 \). In this group, the 5-year PFS was 79% in the XRT group and 64% in the chemotherapy group (hazard ratio 1.85, confidence interval 0.73–4.65; \( P = 0.19 \)). The 5-year overall survival was 76% in the XRT group and 71% in the chemotherapy group (hazard ratio 1.12, confidence interval 0.42–3.04; \( P = 0.82 \)).

The investigators concluded that they observed no statistically significant differences in survival between the two regimens and that adverse effects were not significantly increased in the chemotherapy group. They also found that chemotherapy significantly improved PFS and overall survival in a subgroup of high- to intermediate-risk patients compared with adjuvant pelvic XRT. However, the investigators pointed out that the validity of such a subset analysis is limited.

**NSGO-EC-9501/EORTC-55991**

Early results of a study (NSGO-EC-9501/EORTC-55991) carried out by the Nordic Society of Gynecologic Oncology (NSGO) in collaboration with the European Organization for Research and Treatment of Cancer (EORTC) was presented at ASCO 2007 [15]. They randomised 382 patients between 1996 and 2007; 196 were randomised to adjuvant XRT and 186 to XRT plus chemotherapy. Patients with surgical stage I, II, IIIA (positive peritoneal fluid cytology only) or IIIC (positive pelvic lymph nodes only) were eligible if they, according to departmental guidelines, had a sufficiently high risk for micrometastatic disease to qualify for adjuvant therapy. Most patients had two or more of the risk factors: grade 3, \( \geq 50\% \) myometrial invasion, or DNA non-diploidy, whereas some patients had only one of these. Patients with serous, clear cell, or anaplastic carcinomas were eligible regardless of risk factors. Patients with para-aortic metastases were not eligible. Lymph node exploration at staging surgery was optional. All patients underwent at least TAH-BSO.

Pelvic XRT with or without vaginal brachytherapy was given to a dose \( \geq 44 \text{ Gy} \). Chemotherapy was given before or after XRT. Before August 2004, chemotherapy consisted of four courses of cisplatin \( \geq 50 \text{ mg/m}^2 \) and doxorubicin 50 mg/m² or epirubicin 75 mg/m² (AP). Thereafter, several chemotherapy regimens were allowed, of which AP, paclitaxel 175 mg/m², epirubicin 60 mg/m² and carboplatin AUC 5 (TEcP), and paclitaxel 175 mg/m² and carboplatin AUC 5–6 (TcP) were used.

PFS was the primary end point. The compliance to XRT was very good, over 90% of the patients completed XRT in both arms, whereas compliance to chemotherapy was worse, 27% did not complete chemotherapy. The reasons for the termination of chemotherapy were toxicity in 42% and patient’s own wishes in 38%. The median follow-up time was 4.3 years. The hazard ratio for PFS was 0.62 (confidence interval 0.40–0.97; \( P = 0.03 \)), which translated to an estimated difference in 5-year PFS of 7% from 72 to 79%, and for overall survival 0.65 (confidence interval 0.40–1.06; \( P = 0.08 \)), estimated difference in 5-year overall survival 8% from 74 to 82% both in favour of XRT plus chemotherapy. Although overall there was no significant difference in the distribution of progressions, it is interesting that there was 4% progression in the irradiated area in the XRT group, whereas there was only 1% in the XRT plus chemotherapy group. Totally, 22% progression was registered in the XRT group vs 12% in the XRT plus chemotherapy group.

The investigators concluded that, despite the fact that 27% of the patients randomised to XRT plus chemotherapy received no, or only part of the prescribed chemotherapy, XRT plus chemotherapy was better than XRT alone as adjuvant therapy for patients with early endometrial cancer at high risk for micrometastases.

**RTOG-9708**

The Radiation Therapy Oncology Group (RTOG) has made a pilot study (RTOG-9708) [16] combining adjuvant pelvic XRT with concomitant chemotherapy followed by chemotherapy in grade 2 or 3 endometrial adenocarcinoma with either \( > 50\% \) myometrial invasion, cervical stromal invasion, or pelvic-confined extra-uterine disease. Radiation included 45 Gy in 25 fractions to the pelvis along with cisplatin (50 mg/m²) on days 1 and 28. Vaginal brachytherapy was carried out after the external beam radiation. Four courses of cisplatin (50 mg/m²) and paclitaxel (175 mg/m²) were given at 4-week intervals after the completion of radiotherapy. The investigators found this treatment to be feasible and concluded that locoregional control was excellent in all patients, suggesting additive effects of chemotherapy and radiation while distant metastases continued to occur in more advanced staged patients and that this regimen seemed reasonable to be tested for efficacy in randomised studies.
PORTEC-3

The PORTEC group from the Netherlands has started a randomised study (PORTEC-3) with this concept [17]. They plan to randomise 800 patients with endometrial carcinoma meeting one or more of the following criteria: FIGO stage IB grade 3 disease with documented lymph-vascular space invasion, stage IC–IIA grade 3 disease, stage IIB, IIIA, or IIIC any grade disease (stage IIIA disease based on peritoneal cytology alone allowed if disease is grade 3), or stage IB–III disease with serous or clear cell histology. All patients must have undergone TAH-BSO. Lymphadenectomy and/or full surgical staging is allowed. There should be no residual macroscopic tumour after surgery and no macroscopic stage IIB disease with previous radical hysterectomy.

The patients in the experimental arm are treated with XRT chemotherapy with two courses of cisplatin over 1–2 h on days 1 and 22 and pelvic XRT 5 days a week for up to 6 weeks. At least 3 weeks after the completion of XRT chemotherapy, the patients undergo additional adjuvant chemotherapy comprising TcP every 3 weeks for up to four courses. Patients in the control arm receive XRT as in the experimental arm. The primary end points are overall survival at 5 years and failure-free survival at 5 years. Secondary end points are quality of life, severe treatment-related morbidity, rate of vaginal or pelvic relapse, and rate of distant metastases.

A Cochrane review on adjuvant chemotherapy for endometrial cancer is in preparation [18].

Discussion

There is one study showing the superiority of chemotherapy over WAR [10]. This study is, however, not a pure study of adjuvant therapy because it was done on a mixture of radically operated patients and patients with remaining residual tumour with advanced FIGO stage III–IV endometrial cancer. The radiotherapy was WAR, which is not normally used in the adjuvant situation in early stage endometrial carcinoma. The same tendency to superiority for chemotherapy in all subgroups suggests that there might also be efficacy in the adjuvant situation in early stage cancer, but this remains to be proved.

Two fairly large randomised studies have failed to show any difference in overall survival or PFS between

Table 1 – Randomised studies on adjuvant chemotherapy in early endometrial cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Control arm</th>
<th>Experimental arm</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[12]</td>
<td>FIGO stage I–II (occult) all grades and ≥ 1 of: ≥ 50% myometrial invasion PLN+ or PAN+ Cervical invasion (occult) Adnexal metastases</td>
<td>n = 89 Pelvic XRT 50 Gy ± PA XRT</td>
<td>n = 92 XRT + doxorubicin 45 mg/m² to maximal cumulated dose of 400 (500) mg/m²</td>
<td>5-year overall survival About 60% in both study arms</td>
</tr>
<tr>
<td>[13]</td>
<td>FIGO stage IC grade 3 or stage IIA–B grade 3 with ≥ 50% myometrial invasion or FIGO stage III Non-serous/non-clear cell carcinoma</td>
<td>n = 166 Pelvic XRT 45–50 Gy ± PA XRT 45 Gy</td>
<td>n = 174 Cyclophosphamide 600 mg/m² Doxorubicin 45 mg/m² Cisplatin 50 mg/m² every 4 weeks × 5</td>
<td>5-year Overall survival Chemotherapy 66% XRT 69% 5-yr PFS Chemotherapy 63% XRT 63%</td>
</tr>
<tr>
<td>[14]</td>
<td>FIGO stage IC–IIIC endometrioid carcinoma and: ≥ 50% myometrial invasion and &lt; 75 years old</td>
<td>n = 192 Pelvic XRT 45–50 Gy ± PA XRT ± VBT</td>
<td>n = 193 Cyclophosphamide 332 mg/m² Doxorubicin 40 mg/m² Cisplatin 50 mg/m² every 4 weeks × ≥ 3</td>
<td>5-year Overall survival Chemotherapy 87% XRT 85% 5-yr PFS Chemotherapy 82% XRT 84%</td>
</tr>
<tr>
<td>[15]</td>
<td>Stage I, II, IIIA, IIIC and ≥ 1 of: Grade 3 ≥ 50% myometrial invasion DNA non-diploidy Stage I, II, IIIA, IIIC Serous/clear cell carcinoma</td>
<td>n = 196 Pelvic XRT ≥ 44 Gy ± VBT</td>
<td>n = 186 Cisplatin ≥ 50 mg/m² Doxorubicin 50 mg/m² or epirubicin 75 mg/m² or Paclitaxel 175 mg/m² Epirubicin 60 mg/m² Carboplatin AUC 5 or Paclitaxel 175 mg/m² Carboplatin AUC 5–6 (TcP) every 3–4 weeks × 4</td>
<td>5-year Overall survival Chemotherapy 82% XRT 74% 5-yr PFS Chemotherapy 79% XRT 72%</td>
</tr>
</tbody>
</table>

FIGO, International Federation of Gynecology and Obstetrics; PA, para-aortic; PFS, progression-free survival; PLN+, para-aortal lymph node metastases; PN+, pelvic lymph node metastases; VBT, vaginal brachytherapy; XRT, external radiotherapy.
chemotherapy and XRT [13,14]. Neither the Italian nor the Japanese study was designed or dimensioned to show non-inferiority, which actually means that they are inconclusive [19]. After the presentation of the ASTEC study [20] at ASCO 2007, it seems that adjuvant XRT has no, or at least a very small, effect on overall survival. Hence, adjuvant XRT could serve as a comparison arm simulating no therapy in randomised studies on systemic adjuvant therapy in early endometrial cancer with overall survival as the end point.

It is difficult to find a biological explanation to why the high- to intermediate-risk subgroup in the Japanese study [14] should respond better to chemotherapy than other patients in the study. It is not clear whether this was a pre-planned subgroup analysis. A survival difference in one subgroup with no difference in the total material means that there must be survival differences in the other direction in the other subgroups, which may or may not be significant. Both the low- to intermediate-risk and high-risk subgroups had tendencies to better survival in the XRT arms.

Why are both the Italian [13] and the Japanese [14] randomised studies negative? One reason might be that both used CAP with low dose intensities and low total doses. At the time these studies were planned, CAP was a common regimen in ovarian cancer [21]. There is, however, not much evidence that CAP is an active regimen in endometrial cancer [4]. The two studies had different patient populations, which were both rather heterogeneous as regards the risk profile for micrometastatic disease. The populations were, in varying degrees, 'diluted' by low-risk patients, which is the reason for the different survival in the control groups of the different studies (Table 1). If a new international study on adjuvant therapy of endometrial cancer with high risk for micrometastases could be agreed on, it has to be carried out on a well-defined high-risk patient population with a sufficiently high risk for micrometastatic disease and be adequately powered to be able to detect the small differences in overall survival that could be expected.

Early results from a study comparing XRT plus chemotherapy with XRT showed superior DFS and a trend to a better overall survival [15]. In the Italian study [16] there might also be a tendency to an additive effect of chemotherapy and radiotherapy in the irradiated area. RTOG made a pilot study [16] on adjuvant XRT—chemotherapy plus sequential chemotherapy, and found this concept feasible. The PORTEC group is now conducting a phase III study comparing adjuvant XRT—chemotherapy plus chemotherapy with adjuvant XRT [17]. Surgery was added to radiotherapy in endometrial cancer before randomised studies were implemented as an imperative for changes of standard therapy. The reason was better results for the combination. It has taken half a century to show that radiotherapy adds very little to surgery as far as overall survival is concerned. It now seems that chemotherapy plus XRT might be more effective than XRT alone. The same is probable for XRT—chemotherapy plus chemotherapy. However, we do not know if chemotherapy alone is as effective as chemotherapy plus radiotherapy. We must not repeat the mistake of adding together two toxic therapies without testing if XRT adds anything to chemotherapy by doing the comparison between chemotherapy vs XRT plus chemotherapy.

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