Endometrial cancer: adjuvant treatment of endometrial cancer—radiotherapy, chemotherapy or both

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introduction

Traditionally radiotherapy has been used in a rather inconsistent way as an adjuvant treatment for endometrial cancers. Sometimes vault irradiation has been used, sometimes external beam radiotherapy (EBRT), sometimes both and occasionally chemotherapy. Historically there have even been settings where preoperative radiation was given to downstage tumors but this has generally fallen out of favor. There have been inconsistent approaches in using adjuvant radiotherapy postoperatively to high-risk or intermediate-risk cases (Table 1) and the last few years have seen a refinement in this approach which has been helped by new clinical trial data and meta-analyses that have emerged from a number of important studies.

adjuvant radiotherapy

The first of these studies was over 20 years ago from Aalders [1] in which he showed in a randomized trial that adjuvant external radiotherapy improved local control and reduced local failure but did not improve survival. Sadly this paper tended to be neglected and care remained idiosyncratic. It was not until the beginning of the new century that two more papers confirmed the lack of survival benefit from adjuvant radiotherapy. The first to be reported in full was the PORTEC 1 (Post Operative RadioTherapy in Endometrial Cancer) study [2, 3] which showed a significant reduction in local relapse but with no survival advantage. Following this paper a number of people adopted a policy of using external beam radiotherapy only in intermediate- and high-risk cases and it demonstrated that there was no advantage at all for low-/intermediate-risk patients. Many units adopted the practice of offering EBRT if patients had two of the following risk factors: age over 60 years, outer half involvement (stage 1C) or a grade 3 tumor, and this was a helpful and practical policy. The GOG 99 (Gynecologic Oncology Group) study [4] was eventually published in 2004, although completed some time earlier, and differed in that all the patients underwent lymphadenectomy but again showed no survival advantage, yet with an improvement in local control.

More recently the Medical Research Council (MRC) has completed the ASTEC (A Study of Treatment in Endometrial Cancer) studies, neither of which has been published as yet, but presented at international meetings, the first of which looked at pelvic lymph node dissection (PLND) and has shown no survival advantage when this procedure was added [5]. In May 2007 Orton reported the radiotherapy component of this trial which again showed no survival advantage but also rather curiously showed no advantage for local control [6] against the experience from the four previously presented studies.

Since none of the ASTEC data has been formally published as yet, we rely upon the oral presentations and abstracts for source data but there is an impression that the patients in the ASTEC studies may have had a higher proportion with low-/intermediate-risk disease which may have affected the outcome. The ASTEC study does stand out as the only major study which has failed to show any improvement in local control [2–4, 7–10]. As will be referred to shortly, there is a vigorous debate about the benefits of pelvic (plus or minus para-aortic) lymphadenectomy (PLND). The data from the Surveillance, Epidemiology, and End Results (SEER) analyses seems to suggest that EBRT and PLND may achieve better survival especially in higher-risk patients i.e. stage IC and G3 [11, 12].

For high-risk disease until recently the standard care has been pelvic radiotherapy. Clearly there are advantages as shown in meta-analyses and by the Cochrane group [7, 8]. In the review by Kong there is undoubtedly a benefit in local control when adjuvant pelvic radiotherapy is given but again no survival advantage. An unpublished paper from Soderini from South America was included in their meta-analysis [9]. This is further supported by a presentation at ECCO 2007 from Cornes and Johnson in which they showed that there is up to a 10% survival advantage for patients with IC G3 tumors treated with pelvic radiotherapy [10]. They have also shown that for low-risk patients adjuvant EBRT is probably detrimental whilst for intermediate-risk patients, although there may be a small benefit for some patients, this is offset by additional morbidity leading to an overall neutral effect.

There have also been two papers looking at data from the SEER database [11, 12]. Lee analyzed patients who received pelvic radiotherapy and showed a survival advantage to those who had stage IC grade 3 but failed to show any benefit to other patients, and similarly, Chan, also looking at the SEER analysis, has shown that patients with high-grade IC G3 tumors appeared to benefit. Whilst the number of patients in the SEER study is vast, analyzing over 25 000 patients, it is flawed by the lack of follow up details and data from a limited number of centers so we cannot always be certain how
Given that in the studies discussed above there has been no concomitant chemoradiation followed by three cycles of carboplatin and paclitaxel. This study has recently opened in the Netherlands and is expected to seek international support. Does this mean that we should now adopt sequential chemotherapy and radiotherapy for relapsed disease. When the situation in clear cell and (papillary) serous carcinomas is often viewed differently. Both have a higher risk of extra-uterine spread in the presence of seemingly confined disease to the uterus, thus PLND and adjuvant radiation and/or chemotherapy are more commonly employed. Many use ovarian type schedules in serous carcinomas. Finally one must remember that traditionally the higher risk endometrial cancers usually come from the type 2 category of endometrial cancer [21] and thus are often older, diabetic, hypertensive and obese and thus may not be ideal candidates for more aggressive approaches.

Clear cell and serous carcinoma

The first presentation of the NSGO9505/EORTC55991 study by Hogberg at ASCO 2007 [15] has shown that the use of sequential chemotherapy and radiotherapy with a platinum-anthracycline regime may be the way forward. Again their data has only been presented orally but there is a significant advantage in terms of progression-free survival to the patients who received sequential chemotherapy and radiation compared to radiation alone and at this point there is a trend towards an improvement in survival. This has not yet been substantiated but it is hoped that with further follow up and with more events this might translate into a survival benefit.

Table 1. Simple risk assessment table

<table>
<thead>
<tr>
<th>Stage Grade</th>
<th>Stage 1A</th>
<th>Stage 1B</th>
<th>Stage 1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Low</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Low</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>High</td>
</tr>
</tbody>
</table>

whether the more interesting study would have been to have compared chemotherapy alone with chemoradiation.

There have also been three other important studies that have been reported in the past few years. Maggi on behalf of the Italian group compared pelvic radiation and cisplatin, doxorubicin and cyclophosphamide (CAP) chemotherapy and showed no survival advantage [16] and similarly the Japanese group reported no significant survival difference when pelvic radiotherapy was compared with CAP chemotherapy although the regime was given every four weeks and would be considered suboptimal by today’s standards [17]. The GOG 122 study compared whole abdominal radiation with chemotherapy and suggested that the chemotherapy arm does slightly better but there is a general view that neither arm has done particularly well and that chemotherapy alone may not be the optimal approach [18]. There has been one phase 2 study from the RTOG [19] which shows that concomitant cisplatin and pelvic EBRT can be delivered. The author’s own experience with 40 patients treated with a similar approach is currently being analyzed but shows this is feasible and deliverable.

Historically the treatments used have been a combination of a platinum and anthracycline, usually cisplatin and doxorubicin (AP), but this can be quite a toxic regime and is often poorly tolerated and is not ideal for combining with radiation therapy. Adding paclitaxel (TAP) usually needs growth factors to support the administration. Hoskins showed that carboplatin and paclitaxel (TC) is an active schedule in endometrial carcinoma [20] and many people would view that this is the preferred schedule for treatment although there have been no randomized trials confirming this. In relapsed disease the GOG are currently evaluating TAP versus TC. It is interesting to note that in the PORTEC 3 study this combination has been used in the investigational arm for maintenance treatment.
Table 2. Proposals for adjuvant treatments

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>No adjuvant treatment indicated</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Watch and see but offer salvage EBRT + chemotherapy for local relapse * If LVI discuss chemotherapy PORTEC 3 study Offer chemotherapy and EBRT even if nodes positive Sequential if fit Concomitant cisplatin if moderate fitness EBRT only if less fit</td>
</tr>
<tr>
<td>High risk</td>
<td></td>
</tr>
</tbody>
</table>

EBRT, external beam radiotherapy; LVI, lymphovascular space invasion.

disease is truly localized to the vagina 80–90% of patients should be salvageable.

The greater dilemma is for high-risk patients where the evidence base certainly indicates that adjuvant pelvic radiotherapy should be given for IC G3 cancers but there is emerging data that would indicate that combined chemotherapy and radiation should be offered. The PORTEC 3 study is evaluating this and it will be interesting to see whether there is continuing support for this study or whether the body of opinion moves towards adopting chemoradiation as a standard of care.

At present vaginal brachytherapy would normally only be used in patients with stage 2A or 2B disease but if PORTEC 2 shows no disadvantage perhaps this may be adopted as the standard of care for intermediate-risk disease.

What about the role of chemotherapy? When lymphovascular space invasion is demonstrated in the hysterectomy specimen there must be a significant risk of metastatic relapse and the author of this paper favors giving adjuvant chemotherapy to fit patients with LVS. At present in many parts of Europe, cisplatin and doxorubicin remains the standard of care but there is an increasing shift towards the use of carboplatin and paclitaxel.

Perhaps more controversially, what do we advise for treatment of patients with IC G3 tumors? The NSGO data would support the use of sequential chemotherapy and radiotherapy and many would believe there is sufficient data to accept this as the standard of care. However, the alternative is to encourage entry into the PORTEC 3 study which will hopefully address the question of the benefit of adjuvant chemotherapy and radiation. The window of opportunity to do this study remains open but failure to achieve early high accrual may cause it to fail to make an impact.

disclosures

The author has received lecturing fees and sat on advisory boards for GSK and Schering Plough.

references