Adjuvant treatment for low-risk and intermediate-risk endometrial cancer

The adjuvant treatment of women with low-risk and intermediate-risk endometrial cancer is one of the most controversial topics in gynaecological oncology. Table 2 shows the US National Comprehensive Cancer Network treatment recommendations for stage I and II endometrial cancer.[46] Women with grade 1 and 2 tumours confined to the endometrium have an excellent prognosis and are considered low risk. In one analysis[47] the 10-year recurrence risk for this subset of patients was only 3%. In view of this favourable prognosis, adjuvant therapy is usually withheld.[48–51]

Although definitions vary in individual studies, the remainder of women with stage I and II tumours are considered intermediate risk. So far, no study of adjuvant treatment has convincingly shown survival benefit in this subgroup of women. In patients who have undergone comprehensive staging, survival is favourable even without further therapy.[52] Radiation has been the most frequently prescribed treatment; however, two studies[53,54] have examined the use of chemotherapy either alone or in combination with radiation for intermediate-risk patients. Radiation reduces the risk of local, pelvic recurrence but does not improve survival in women with stage I or II endometrial cancer (table 3).[55–59] Investigators for the Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC)-1 trial randomly assigned 715 patients with stage IB grade 2–3 tumours or stage IC grade 1–2 tumours to either observation or whole pelvic radiotherapy. After 10 years of follow-up survival did not differ between groups but pelvic radiation reduced the risk of vaginal recurrence from 15% to 4%.[55] A Gynecologic Oncology Group trial[56] done in the USA in women with early-stage disease who had undergone lymphadenectomy as part of their treatment had similar findings.

The inability of adjuvant pelvic radiotherapy to improve survival stems partly from the fact that many recurrences occur at the vaginal cuff and can be salvaged with radiotherapy at the time of recurrence. However, the results from these trials must be interpreted with caution because many patients included in the studies were at low risk of death from endometrial cancer.[55–58] These trials might therefore not have the power to identify a survival advantage for early-stage patients at greatest risk.

In view of these limitations, investigators have attempted to identify subgroups of patients with early-stage endometrial cancer who might benefit from radiotherapy. An analysis of more than 21000 patients in the US National Cancer Institute's Surveillance, Epidemiology, and End Results database showed that radiation improved survival for women with stage IC tumours.[60] Results of two meta-analyses[61,62] have suggested that radiation is associated with improved survival for patients with stage IC, grade 3 neoplasms.

Pelvic radiotherapy, especially after lymphadenectomy, can be associated with pronounced adverse effects.[55,56] 25% of 354 patients in the radiotherapy group of PORTEC-1 had late complications.[55] To decrease the morbidity associated with pelvic radiotherapy while attempting to preserve the benefits of decreasing locoregional recurrences, vaginal brachytherapy is now widely used for intermediate-risk endometrial cancer.[62] Vaginal brachytherapy is administered in the outpatient setting with a vaginal cylinder. With high-dose rate schedules, three fractions of 7 Gy each are delivered at 1 week intervals. A randomised trial comparing[59] whole pelvic radiotherapy and vaginal brachytherapy for intermediate-risk endometrial cancer (PORTEC-2) showed no difference in survival between the two methods. The investigators noted that although the vaginal recurrence rate was 1·8% for brachytherapy compared with 1·6% for external beam radiation, pelvic recurrences were more frequent with brachytherapy (3·8% *vs* 0·5%).[59]

Endometrial cancer was previously thought to spread predominantly through lymphatic dissemination, but clinicians now recognise that even women with tumours

	Sample size	Inclusion criteria	Surgery	Treatment	Locoregional recurrence	Overall survival
Norwegian Radium Hospital[57]	540	Stage I (all)	TAH or BSO	Brachytherapy *vs* brachytherapy and pelvic radiotherapy	7% *vs* 2% (5 year) p<0·01	89% *vs* 91% (5 year) p=NS
PORTEC-1[55]	715	Stage IB (grade 2, 3), stage IC (grade 1, 2)	TAH or BSO (LNS allowed)	Observation *vs* pelvic radiation	14% *vs* 4% (5 year), p<0·0001	85% *vs* 81% (5 year), p=0·31
GOG 99[56]	392	Stage IB, stage IC, stage II occult	TAH or BSO or LNS	Observation *vs* pelvic radiation	12% *vs* 3% (2 year), p=0·007	86% *vs* 92% (4 year), p=0·55
ASTEC[58]	905	Stage IA or IB (grade 3), IC, IIA	TAH or BSO with or without LNS	Observation *vs* pelvic radiation	6·1% *vs* 3·2% (5 year), p=0·02	84% *vs* 84% (5 year), p=0·31
PORTEC-2[59]	427	Stage IC (grade 2, 3, age >60 years), IB (grade 3, age >60 years), IIA	TAH or BSO with or without LNS	Brachytherapy *vs* pelvic radiation	5·1% *vs* 2·1% (5 year), p=0·42	86% *vs* 82% (5 year), p=0·66

TAH=total abdominal hysterectomy. BSO=bilateral salpingo-oophorectomy. LNS=lymph node surgery. NS=not significant.

Table 3: Randomised controlled trials of adjuvant therapy for intermediate-risk endometrial cancer

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that seem confined to the uterus are at risk of distant disease. A study of women with high-grade, deeply invasive tumours who all received pelvic radiotherapy showed that nearly a third developed distant metastases.[63] The high rate of systemic failure and the success of chemotherapy for advanced-stage endometrial cancer provide strong rationale for the investigation of adjuvant chemotherapy in women with uterine-confined disease.[53,54,64] The Japanese Gynecologic Oncology Group compared pelvic radiotherapy and chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in a cohort of women with stage IC–IIIC endometrial cancer. Although survival was equivalent for the two methods overall, the investigators noted a survival advantage in the group of women whom they described as high-to-intermediate risk (stage IC, >70 years of age, or grade 3; or stage II or positive cytology with >50% myometrial invasion).[53]

Several groups are investigating chemotherapy in combination with radiation for intermediate-risk endometrial cancer.[65,66] The European Organisation for Research and Treatment of Cancer and Nordic Society of Gynecological Oncology reported results of a trial[67] comparing adjuvant radiation to chemotherapy (various regimens) and radiation in patients with stage I–IIIC endometrial cancer. The hazard ratio for progression-free survival was 0·64 (95% CI 0·41–0·99) in favour of the combination regimen. 27% of 186 patients in the chemotherapy group did not complete treatment.[67] The Gynecologic Oncology Group's protocol for the adjuvant treatment of high-intermediate-risk endometrial cancer compares whole pelvic radiotherapy with the combination of vaginal brachytherapy and carboplatin and paclitaxel (Gynecologic Oncology Group protocol 249). The PORTEC-3 trial compares pelvic radiotherapy with radiation plus chemotherapy for women with high-intermediate-risk and high-risk disease. Future trials will probably continue to explore the role of chemotherapy for intermediate-risk endometrial cancer. The Japanese Gynecologic Oncology Group is doing a randomised trial to establish the most feasible chemotherapy regimen without radiotherapy for women with intermediate-risk endometrial cancer.[68]

Adjuvant treatment for advanced-stage disease

Adjuvant chemotherapy is now the mainstay of treatment for women with stage III and IV endometrial cancer. A trial[69] of whole abdominal radiotherapy versus chemotherapy with cisplatin and doxorubicin in patients with stage III and IV disease showed the superiority of chemotherapy to radiation. 5-year survival was 53% in patients given chemotherapy compared with 42% for the radiation group.[69] On the basis of these findings, chemotherapy was rapidly incorporated into the care of women with advanced-stage endometrial cancer.

As in the treatment of intermediate-risk endometrial cancer, clinicians frequently use multimodality therapy for women with advanced-stage disease.[70,71] Multimodality therapy combines the systemic effects of chemotherapy with the improved local control provided by radiation.[70,71] The subgroups of patients most likely to benefit from combination therapy, the optimum chemotherapeutic agents, and the ideal sequencing are under active investigation. The Gynecologic Oncology Group prospectively examined radiation in combination with doxorubicin and cisplatin with or without paclitaxel in the adjuvant treatment of women with stage III and IV endometrial cancer. The addition of paclitaxel had no effect on survival but was associated with increased toxic effects.[72]

Recurrent disease

Women with recurrent endometrial cancer are a highly heterogeneous population, ranging from patients affected by an isolated vaginal relapse amenable to curative therapy to women presenting with widespread disease in whom palliation constitutes the mainstay of treatment. As such, treatment is highly individualised. Surgery, radiation, chemotherapy, and hormonal therapy are all used for recurrent endometrial cancer.

Radiation is the treatment of choice for women who have a relapse at the vaginal cuff after surgery.[73,74] 2-year survival after an isolated recurrence at the vaginal cuff is as high as 75%.[56,73,74] Patients with vaginal recurrences who have previously received radiotherapy are candidates for surgical resection. Selected patients with large pelvic recurrences might also be candidates for surgery or radiotherapy. Other radical surgical approaches such as secondary cytoreduction, pelvic exenteration, or laterally extended endopelvic resection might be considered in highly selected patients with locally advanced disease and good performance status in whom cure might be possible.[75]

Endometrial cancer is hormonally responsive, and several endocrine therapies have been examined for women with recurrent disease. Progestagens and tamoxifen are the most commonly used agents; aromatase inhibitors and gonadotropin-releasing hormone analogues have also been assessed but have shown less antitumoral activity.[76–79] Progestagens have shown response rates of 15–30%, with median overall survival of 7–11 months. Most responses are partial and of short duration. Response rates tend to be higher in women with well differentiated tumours and in those with neoplasms that express the progesterone receptor than in other types of tumour.[77,80] In the Gynecologic Oncology Group's series, 17 of 46 (37%) women with progesterone-receptor-positive tumours responded to progesterone compared with only seven of 86 (8%) of those with progesterone-receptor-negative neoplasms.[77] Several trials have examined various dosing regimens and endocrine combinations: low-dose progestagen regimens seem to be as effective as higher-dose regimens, but are associated with fewer toxic effects; and the combination of tamoxifen with a progestagen does not seem to confer

benefit to progestational therapy alone.[77,81-85] Endocrine therapy is especially attractive in women with medical comorbidities because it is typically well tolerated and has a favourable side-effect profile.

Cytotoxic chemotherapy is frequently given to women with systemic disease. Although several chemotherapeutic agents have been assessed, doxorubicin and cisplatin have traditionally been regarded as the most active single agents. Response rates for single-agent doxorubicin are reported to range from 17% to 25%.[86-89] Although the response rate for the combination of doxorubicin and cisplatin is better than that for doxorubicin alone, survival is much the same for the combination regimen and single-agent treatment.[88,90]

Interest has also focused on the incorporation of paclitaxel into the treatment of recurrent endometrial cancer. Combinations of paclitaxel with a platinum analogue, cisplatin or carboplatin, have shown response rates of more than 40%.[91,92] The Gynecologic Oncology Group investigated doxorubicin in combination with paclitaxel as an alternative to doxorubicin and cisplatin.[93] The two combinations showed similar response rates and survival.[93] The same group compared doxorubicin and cisplatin with a three-drug regimen consisting of doxorubicin, cisplatin, and paclitaxel.[94] The objective response rate was improved from 34% to 57% with the three-drug regimen and overall survival was improved from 12·3 to 15·3 months. The triple regimen was associated with substantial toxic effects—more than a quarter of patients assigned to doxorubicin, cisplatin, and paclitaxel had grade 2 neuropathy, and 12% had grade 3 neuropathy.[94] In view of the substantial side-effect profile of doxorubicin, cisplatin, and paclitaxel, many clinicians treat elderly women who have recurrent endometrial cancer with carboplatin and paclitaxel or a less toxic doxorubicin-containing doublet. The Gynecologic Oncology Group is doing a phase 3 trial comparing doxorubicin, cisplatin, and paclitaxel with carboplatin and paclitaxel (Gynecologic Oncology Group protocol 209).

Preliminary data for several molecularly targeted agents for endometrial cancer are emerging. The PI3K/Akt/mTOR pathway is frequently upregulated in women with endometrial cancer because of loss of the tumour suppressor gene *PTEN*.[95] Inhibitors of the mammalian target of rapamycin (mTOR) have shown promising early results.[96,97] The mTOR inhibitor temsirolimus was associated with a 26% response rate in chemotherapy naive patients.[98] In patients with previous treatment, investigators noted a 4% (one of 25 patients) response rate with disease stabilisation in 48% (12 of 25).[97] Although epidermal growth factor receptor is frequently expressed in normal endometrium and in endometrial cancer, use of erlotinib, an inhibitor of the receptor, was associated with a response rate of only 13%.[99,100] Similarly, although HER-2/neu is frequently overexpressed or amplified in endometrial cancer, no responses to the monoclonal anti-HER-2/neu antibody trastuzumab were reported in a phase 2 trial.[101,102] Angiogenesis and vascular endothelial growth factor signalling also seem to have a key role in endometrial cancer progression.[103,104] Although a phase 2 trial of the oral, multitarget tyrosine kinase inhibitor sorafenib showed disappointing results, several trials of the antivascular endothelial growth factor monoclonal antibody bevacizumab are continuing.[105]

Conclusions

The past decade has witnessed several remarkable advances for endometrial cancer. An improved understanding of the molecular biology of endometrial cancer, the introduction of less morbid minimally invasive surgical approaches, and the more routine use of chemotherapy have all improved the outcomes of women with endometrial cancer. Further trials to refine adjuvant treatment strategies and to establish the efficacy of target therapeutics are underway and will probably improve the treatment of endometrial cancer.

Contributors

All authors contributed to the content development, reviewed the published work, and drafted and approved the final version of the report.

Conflicts of interest

JDW has received research funding from Genentech and Merck, and payment for lectures from Precision Therapeutics. TJH has been a consultant for Genentech, GlaxoSmithKline, Johnson & Johnson, Pfizer, Roche, Bayer, Sanofi-Aventis, and Precision Therapeutics, and has received payment for lectures from Amgen, GlaxoSmithKline, Johnson & Johnson, Lilly, and Merck. NIBM, KF, and JS declare that they have no conflicts of interest.

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