

# THE EVOLVING MANAGEMENT OF ENDOMETRIAL CANCER

## The BCCA philosophy

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### Top-line summary

Endometrial cancer, the fourth most common cancer in Canadian women, is often curable. About 20% of cases remain incurable, however, a rate that has changed very little in the last 10–15 years. The main treatment is surgery, with radiation therapy if there appears to be risk of local spread. Women at high risk of spread to distant sites are given chemotherapy to improve their survival odds. Examination of lymph nodes in the pelvic and para-aortic areas has traditionally been recommended, but recent evidence shows that this practice does not prolong survival. Surgical stage, tumour grade, histologic type and presence or absence of lymphovascular spread are the current means of evaluating risk, but they result in a substantial number of women receiving chemotherapy when they don't actually need it. This article summarizes the policies and practices of the British Columbia Cancer Agency, and highlights areas where better treatments and criteria for determining risk of disease recurrence and metastatic spread are needed.

The incidence of endometrial cancer in Canada is increasing as the population ages. With an estimated 4100 new cases in 2007, a woman's lifetime risk is 2.4%.<sup>1</sup> Endometrial cancer is the fourth most common cancer in women behind breast (22,300 new cases), lung (10,900) and colorectal (9400).<sup>1</sup>

The great majority of women with endometrial cancer, about 80%, will be cured because the cancer is both well differentiated and confined to the uterus, and therefore curable through surgery. Luckily, symptoms such as abnormal bleeding often lead to early detection and successful therapy. However, this 80% cure rate has improved very little over the years: the annual average reduction in mortality from 1994 to 2003 was only 0.2%. To do better, the 20% of patients with disease not confined to the uterus need to be identified and given additional effective therapy following their initial surgery. Chemotherapy is essential for eliminating disseminated disease, which ultimately is the fatal component. In the absence of 100% effective chemotherapy, radiation is needed to improve local control. Evolution in the management of endometrial cancer has thus focused on efforts to identify those women with no risk of extra-uterine disease, who will be cured by hysterectomy alone, and to offer the rest effective chemotherapy with or without radiation therapy (RT). Some oncologists continue to recommend more aggressive surgical intervention targeting lymph node involvement, but in our opinion this is of limited value. This article summarizes the policies and practices of the British Columbia Cancer Agency (BCCA), with relevant supporting evidence.

#### IDENTIFYING RISK OF EXTRAUTERINE DISEASE

In the absence of molecular tests to evaluate risk, we rely on the prognostic information provided by the old standbys of staging and pathology, i.e. the combination of surgical

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stage — essentially depth of invasion and extrauterine spread to nodes, cervix and adnexae (ovaries and fallopian tubes); grade; histology; and the presence of lymphovascular space invasion (Table 1). This information reliably and reproducibly identifies both those with low-risk, surgically curable tumours and those at higher risk due to either macroscopic, disseminated disease (i.e. Stage III and IV) or earlier stage disease with an aggressive histology. Certain histologic subtypes have a markedly worse prognosis in the early stages. Papillary serous (PS), clear cell (as assessed by International Federation of Gynecology and Obstetrics [FIGO] criteria) and malignant mixed Mullerian tumours (MMMTs) have 5-year survival rates for Stage I disease of

**TABLE 1. FIGO Surgical staging classification and survival in patients treated 1990–1992**

stage	characteristics	5-year overall survival
IA	tumour limited to the endometrium	91%
IB	tumour invasion < half of the myometrium	88%
IC	tumour invasion ≥ half of the myometrium	81%
IIA	endocervical glandular involvement only	77%
IIB	cervical stromal invasion	67%
IIIA	tumour invasion of serosa of the corpus uteri and/or adnexae and/or positive cytology	60%
IIIB	vaginal metastasis	41%
IIIC	metastasis to pelvic and/or paraaortic lymph nodes	52%
IVA	tumour invasion of bladder and/or bowel mucosa	20%
IVB	distant metastasis, including intra-abdominal	5%

Source: FIGO data

**TABLE 2. Modified BCCA treatment algorithm**

stage & risk	EBRT*		vaginal brachytherapy†	carboplatin + paclitaxel‡
	pelvis†	para-aortics		
<b>I low-risk</b>				
IA, Grade 1–2	–	–	–	–
IB, Grade 2	–	–	+/-	–
<b>intermediate-risk</b>				
IA–B, Grade 3 IC, Grade 1–2 any substage with lymphovascular invasion	+/-	–	+/-	–
<b>high-risk</b>				
IC, Grade 3 PS or MMMT histology (except 1A)	+	–	+	3 cycles pre-radiotherapy
<b>II low-risk</b>				
Grade 1–2	+	–	+	–
<b>high-risk</b>				
Grade 3 PS, MMMT or clear cell histology	+	–	+	3 cycles pre-radiotherapy
<b>III low-risk</b>				
IIIA, Grade 1–2	+	–	+	–
<b>high-risk</b>				
IIIB–C, all grades; IIIA, Grade 3: MMMT, PS or clear cell histology	+	if involved	+	3 cycles pre-radiotherapy
<b>IV all grades</b>	if all known disease is radio-encompassable		–	6 cycles

\*EBRT = external beam radiation therapy

†+/- either at diagnosis or upon release

‡paclitaxel 175 mg/m<sup>2</sup> over 3 hours then carboplatin AUC 5–6

72%, 80% and 61% respectively and for Stage II of 61%, 65% and 19%.<sup>2</sup> Women with Stage IA PS and MMMT types do better (unpublished BCCA data), so are as yet not routinely offered chemotherapy. The challenge is to identify those with apparent uterine-confined disease (i.e. Stage I and II) who already have microscopic dissemination beyond the reach of the surgeons and radiation oncologists. Using clinical prognostic factors we can identify a group with a higher risk of relapse, in the range of 20% to 40%. At the BCCA we offer chemotherapy to all of these higher-risk patients, recognizing that not all truly need it.

British Columbia's provincial policy is currently being revised in light of the recent data described in this article, and will likely offer chemotherapy to women with earlier-stage, high-risk disease and eliminate the use of lymph node dissection. Table 2 outlines our treatment recommendations incorporating these modifications. All patients undergo initial simple hysterectomy and bilateral salpingo-oophorectomy. For those with documented widespread disease (Stage III and IV), we recommend debulking surgery if maximal cancer removal is thought to be feasible, as is done in ovarian cancer. Subsequently, we offer radiation and chemotherapy based on likely sites of relapse. The BCCA philosophy is to add

chemotherapy if the predicted chance of death is  $\geq 25\%$  and RT if the risk of local relapse is  $\geq 10\%$ .

## DOES LYMPHADENECTOMY ADD VALUE?

There is ongoing debate as to the extent of surgery required. All the academic groups and opinion leaders recommend simple hysterectomy and bilateral salpingo-oophorectomy. Opinions differ, however, about the value of pelvic and para-aortic lymphadenectomy, which FIGO mandated in 1998 as a component of full surgical staging. This entailed total abdominal exploration, peritoneal washings, and biopsy of abnormal areas, cervical lymph nodes and normal-appearing pelvic and para-aortic lymph nodes (Table 1). Proponents of lymph node dissection cite a therapeutic effect and treatment-modifying benefit accruing to those with early-stage disease, by identifying women with lymph node involvement who thus need additional therapy, and also by identifying the lymph node-negative women who need no further therapy as they are cured by surgery alone.

Retrospective studies showed an apparent survival benefit with pelvic lymph node dissection but this was not confirmed by the prospective ASTEC study (A Study in the Treatment of Endometrial Cancer).<sup>3</sup> This trial randomized 1408 women regarded as Stage I or II preoperatively to total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic node dissection. High-risk patients were subsequently randomized to pelvic external beam radiation therapy (EBRT) or observation. Survival at 3 years was 89% for those with node dissection and 88% for those without. Systemic disease, not local relapse, was the major cause of death: the purely local measure of lymph node dissection was thus doomed to failure. Further, as discussed later, local failure is usually pelvic, not nodal.

If there is no therapeutic benefit, does lymphadenectomy offer any additional prognostic or treatment-changing role over and above that available from pathologic review of the hysterectomy specimen? The Gynecologic Oncology Group (GOG)-33 trial was a prospective evaluation of full surgical staging in women with apparent Stage I and II disease.<sup>4</sup> The risk of extrauterine spread correlated with depth of uterine invasion and grade. Overall, 11% of patients had nodal involvement (51% pelvis only, 31% pelvis and para-aortic nodes, and 17% para-aortic only). Three-quarters of all patients fell into a low-risk group (Stage IA, all grades; or IB, Grades 1 and 2) and had less than a 7% risk of nodal involvement. This small risk does not justify the costs and morbidity associated with node dissection, or even with pelvic radiation. The remaining 25% of Stage I patients

**TABLE 3. Randomized trials of chemotherapeutic agents in advanced or recurrent endometrial carcinoma**

regimen (year), reference	response rate	median overall survival (months)	statistical significance (p-value)
doxorubicin (1984) <sup>12</sup>	22%	6.7	ns
doxorubicin + cyclophosphamide	33%	7.3	
doxorubicin (2003) <sup>13</sup>	17%	7	ns
doxorubicin + cisplatin	43%	9	
doxorubicin (2004) <sup>14</sup>	25%	9.2	ns
doxorubicin + cisplatin	42%	9	
doxorubicin + cisplatin (2003) <sup>15</sup>	46%	11.2	ns
circadian-timed doxorubicin + cisplatin	49%	13.2	
doxorubicin + cisplatin (2004) <sup>16</sup>	40%	12.6	ns
doxorubicin + paclitaxel	43%	13.6	
doxorubicin + cisplatin (2004) <sup>17</sup>	34%	12.3	0.037
doxorubicin + cisplatin + paclitaxel	57%	15.3	

(Stage IB or C with Grade 3 disease, and Stage IC with any grade) are a higher-risk group, with risk of recurrence of 25% to 40%. A negative lymph node dissection does not help to define the 60% to 75% of “no-risk” individuals within this higher-risk cohort. Relapse rates in women in the PORTEC study (Post Operative Radiation Therapy in Endometrial Cancer), in which all women had normal-appearing nodes and lymphadenectomy was not performed, were as follows: those with Stage IB, Grade 3 disease (with no pelvic radiation) had 14% vaginal, 0% pelvic and 20% distant recurrence;<sup>5</sup> for Stage IC, Grade 3 (in which RT was used, thus at least halving relapse rates) relapse rates were 5% vaginal, 8% pelvic and 31% distant.<sup>6</sup> Thus, the majority of relapses are extra-pelvic and not predictable by node dissection. Local relapse, while not as frequent as distant relapse, is still a problem but 75% of these local relapses are vaginal, not pelvic, and cannot be predicted by pelvic node dissection. It makes more sense to offer pelvic radiation to the whole group, as the radiation field includes the vagina and pelvic side walls as well as the lymph nodes.

Would a negative pelvic lymphadenectomy eliminate the need for EBRT of the pelvis? The lower-morbidity procedure of vaginal brachytherapy could then be used for vaginal control. Alternatively, given that isolated pelvic relapse is curable with EBRT, a watchful waiting approach could be adopted. The answer is a qualified yes. In GOG-99, which included both low- and high-risk early-stage patients, only 2% of the whole cohort had pelvic recurrence after negative lymphadenectomy. For the higher-risk cohort, this study did not break down local relapse rates into vaginal vs pelvic locations, but if the same ratio applies

as seen in the whole group, the rate of pelvic relapse would still be very low, at about 4%.<sup>7</sup>

### THE ROLE OF RADIATION

Until we have 100% effective chemotherapy, EBRT remains valuable in women who have endometrial cancer with microscopic pelvic spread. Compared to surgery alone, it significantly reduces local recurrence but does not impact survival and is associated with increased rates of chronic bowel dysfunction. Three randomized trials of surgery vs surgery + pelvic radiation in women with uterus-confined disease (Stage I or II) considered at risk for occult pelvic spread have been carried out with similar results.<sup>5,7,8</sup> RT reduced the local recurrence rate to 2% to 4% from an already low rate of 7% to 14%, a mean absolute fall of 7%. Five-year overall survival, however, was 81% to 91% with no difference if radiation was added. These studies were flawed in that most women were not at high risk of recurrence, and the majority who died did so from intercurrent illness, not endometrial cancer. While post hoc subset analysis identified truly higher-risk groups in whom there were survival differences, these were not statistically significant. It is impossible to determine if this was due to small sample size and thus an underpowered trial.

The GOG identified 4 adverse factors associated with relapse: age > 70, lymphovascular invasion, deep myometrial invasion and Grade 2–3 tumour status. The high-risk groups, all known to be pelvic node-negative at lymphade-

nectomy, were those of age > 70 years plus 1 other factor; age 50–70 plus 2 factors; or presence of all 3 factors regardless of age. RT reduced the rate of death from 17% to 10% in the high-risk cohorts. The rate of pelvic relapse was high, indicating that negative pelvic node status did not correlate well with low risk of pelvic relapse.<sup>7</sup> This can be contrasted to results reported by the PORTEC group in similar patients. A subset with deeply invasive (Stage IC), Grade 3 endometrial cancers was followed as part of the PORTEC study.<sup>6</sup> These women all had macroscopically normal pelvic nodes and all received pelvic radiation, without formal node dissection. Their rate of locoregional relapse was 13%,<sup>6</sup> as compared to 27% in the study reported by Keys et al in a lower-risk group treated with lymphadenectomy alone.<sup>7</sup> Distant relapse occurred in 31%, and 30% of the Stage IC, Grade 3 cohort died of endometrial cancer.<sup>6</sup> Such failure rates in these higher-risk cohorts demonstrate the need for adjuvant treatment.

In the absence of fully effective chemotherapy, patients with advanced-stage disease (Stage III and IV) may also derive benefit from pelvic radiation, which reduces the rate of local relapse. Two randomized studies compared cisplatin + doxorubicin combinations to RT including the pelvis. Radiation decreased the rate of pelvic relapse by about 5% overall, from 16% to 12%<sup>9</sup> and 18% to 13%.<sup>10</sup> More effective radiation is required; an obvious next step to increase efficacy would be to give concurrent platinum or platinum-based chemotherapy with pelvic radiation, as is done in

cancer of the cervix — an approach that will be investigated in the proposed PORTEC-3 study.

**TABLE 4. Phase III studies of radiation therapy (RT) vs chemotherapy + RT and chemotherapy vs RT**

author, year, reference	disease types	regimens (number of patients)	5-year progression-free survival	5-year overall survival
Hagberg, 2007 <sup>19</sup>	high-risk Stage I, II IIIA, IIIC	pelvic RT (n = 190)	75%	-
		pelvic RT + platinum combination (n = 177)	82%	-
Randall, 2006 <sup>9</sup>	Stage III–IV (abdominal only), residual < 2 cm	whole abdominal + pelvic ± para-aortic RT (n = 202)	38%	42%
		doxorubicin + cisplatin (n = 194)	50%	55%
Sagae, 2005 <sup>20</sup>	Stage II–III (Stage IC: no differences found)	pelvic RT (n = 33)	64%	80%
		doxorubicin + cisplatin + cyclophosphamide (n = 41)	84%	97%
Maggi, 2006 <sup>10</sup>	Stage IC, Grade 3; Stage II, Grade 3; Stage III	pelvic ± para-aortic RT (n = 168)	63%	69%
		doxorubicin + cisplatin + cyclophosphamide (n = 177)	63%	66%


### WHICH CHEMOTHERAPY REGIMEN?

From randomized trials we know that the median survival of women with advanced (Stage III or IV) or recurrent endometrial cancer (with the exception of isolated vaginal vault relapse) is approximately 1 year. Because these women have abdominal or distant sites of disease, optimal treatment requires cytotoxic therapies. While many chemotherapeutic agents have been studied in Phase II studies, the most active single agents appear to be the platinum, taxanes and anthracyclines, all providing response rates of approximately 20%.<sup>11</sup> Phase II studies of multi-drug regimens have routinely achieved even higher response rates, with the highest responses, 40% to 67%, obtained with regimens containing a platinum-taxane combination.<sup>11</sup>

It has been challenging to demonstrate a survival benefit, as opposed to improved response rates,

from a particular regimen in patients with advanced or recurrent endometrial carcinoma. Published trials have compared either a combination regimen to an active single agent (most commonly doxorubicin) or to another active combination regimen, as shown in **Table 3**, page 10. Historically the preferred regimen(s) have gone from doxorubicin alone to doxorubicin + cisplatin and, recently, platinum + taxane. To date, only 1 randomized trial has demonstrated improvement in patient survival due to combination chemotherapy. In the GOG-177 study, 273 patients were randomized between paclitaxel + doxorubicin + cisplatin (TAP) and doxorubicin + cisplatin (AP). The triplet regimen required granulocyte colony-stimulating factor (G-CSF) support and was delivered over 2 days, with paclitaxel given on Day 1 and doxorubicin and cisplatin given on Day 2, in order to avoid the cardiotoxicity reported in breast cancer studies when paclitaxel and doxorubicin were given on the same day. TAP resulted in a near doubling of the response rate, from 34% to 57%, and a statistically significant improvement in overall survival of 3 months from 12.3 to 15.3 months ( $p = 0.013$ ). TAP therefore represents the most active regimen with Phase III evidence in advanced endometrial cancer. However, the high rate of neurotoxicity (40% in the TAP arm vs 5% in the AP arm), gastrointestinal toxicity and expense associated with the use of G-CSF, with only a modest absolute improvement in survival, has prevented TAP from being readily accepted as the standard of care. The GOG is further testing this regimen in a randomized trial of women with advanced and recurrent endometrial carcinomas against the widely used and well tolerated doublet of carboplatin and paclitaxel (PT), a regimen with Phase II data showing a similar response rate to TAP of approximately 60%.<sup>18</sup> PT (carboplatin AUC 5–6 + paclitaxel 175 mg/m<sup>2</sup> over 3 hours every 3–4 weeks) has the advantages of being easily administered and generally well tolerated, with lower incidence and severity of neurotoxicity, and being very familiar to medical and gynecologic oncologists. As such, it has been adopted as our standard regimen at the BCCA.<sup>18</sup>

## DOES CHEMOTHERAPY IMPROVE SURVIVAL?

Three Phase III studies (**Table 4**, page 11) provide data comparing platinum-based combinations to radiotherapy,<sup>9,10,20</sup> and 1 compares a platinum combination + radiotherapy to radiotherapy alone.<sup>19</sup> Less effective chemotherapy (cisplatin + doxorubicin with or without cyclophosphamide) was used in all but the Hogberg study,<sup>19</sup> in which the patients enrolled later could receive a platinum + taxane regimen. Three of the 4 showed statistically significant improvements in 5-year progression-free survival, with absolute benefits of 7% to 20%. Despite this, 16% to 50% of women in the chemotherapy arms still relapsed, with worse results for higher-stage patients. Platinum + taxane combinations will improve this somewhat but, as with nearly all solid cancers, additional approaches specific to molecular targets such as the VEGF, EGFR and Akt pathways will be required. A number of Phase I–II trials investigating the activity of new agents are planned or underway. 

## Disclosure

Drs. Hoskins and Tinker report having no potential conflicts of interest related to this article.

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