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REVIEW ARTICLE

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## Adjuvant Treatment for Endometrial Carcinoma

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### ABSTRACT

*The prognostic factors for patients with endometrial cancer include International Federation of Gynecology and Obstetrics stage, age, resection margin, lymphovascular invasion, and histology type. Patients with high-risk disease may develop local, regional, and/or distant recurrences. Traditionally, whole pelvic radiotherapy is the treatment option for patients with risk factors that predict pelvic recurrence, in particular, deep myometrial invasion or serosal extension, high-grade disease, cervical or adnexal involvement, and close margins. Several randomised studies confirmed better pelvic control for patients with clinically or surgically staged intermediate- to high-risk early-stage disease after whole pelvic radiotherapy, but not survival, when compared with observation alone, and at the price of increased severe late toxicities. Several retrospective studies showed that good pelvic control could be achieved with vaginal brachytherapy alone for patients with surgically staged intermediate- to high-risk disease, and with a better toxicity profile when compared with whole pelvic radiotherapy. In addition, the preliminary results of several randomised studies show that adjuvant chemotherapy may offer survival benefit for patients with intermediate- to high-risk disease. The role of various adjuvant treatments, including vaginal brachytherapy, retroperitoneal surgery, chemotherapy, and hormonal therapy, will be discussed in this review.*

*Key Words:* Brachytherapy; Endometrial neoplasms; Radiotherapy, adjuvant; Toxicity

### INTRODUCTION

Endometrial carcinoma is a common female cancer in the western world. According to the Hong Kong Cancer Registry, endometrial carcinoma was the ninth commonest female cancer in 1999, but increased to fourth place in 2005.<sup>1</sup> The change of lifestyle of the female population is thought to be one of the explanations for this increase. Endometrial carcinoma was the 17th most common cause of cancer death in 2005, despite most patients being diagnosed at an early stage.<sup>1</sup> Surgery, consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy, is the primary treatment modality for operable disease.

Patients with high-risk endometrial carcinoma may develop local, regional, and/or distant relapses. In 1987, the surgical pathological study of the Gynecologic

Oncology Group (GOG) identified several risk factors that could predict for pelvic or para-aortic lymph node involvement.<sup>2</sup> These risk factors included deep myometrial invasion, grade 3 disease, cervical involvement, positive peritoneal washing, adnexal involvement, and capillary-like space invasion. Patients with both deep myometrial invasion and grade 3 disease had a 34% and 23% risk for pelvic and para-aortic lymph node involvement, respectively. In a subsequent GOG study, patients with positive para-aortic lymph node involvement had poor 5-year disease-free survival (36%).<sup>3</sup> Most of these factors were incorporated into the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system.<sup>4</sup> As well as FIGO staging, older age and poor histology such as papillary serous and clear cell carcinoma are poor prognostic factors.<sup>5,6</sup>

Whole pelvic external beam radiotherapy (WPRT) has been the standard postoperative adjuvant treatment for high-risk patients to reduce locoregional recurrences. However, the survival benefit after radiotherapy has never been shown in randomised studies, although the associated late complications have been consistently reported.<sup>7-9</sup> Together with an increase in the practice of

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surgical staging and awareness of early promising results of chemotherapy, the role of adjuvant WPRT has been the subject of much debate in recent years.

## EARLY-STAGE DISEASE

### Risk Groups

The choice of adjuvant treatment for patients with cancer of the uterine corpus depends on which risk group the patient belongs to. Although there is a slight difference in the definition of risk, patients with clinical stage IA grade 1 or 2 and stage IB grade 1 or 2 are classified as low risk in most studies (Table 1).<sup>10-13</sup> The overall recurrence rate for patients at low risk has been consistently found to be approximately 5% or lower, irrespective of whether or not adjuvant radiotherapy was given. Most recurrences occur at the vaginal vault only.

The definition of intermediate or high risk for patients with early-stage disease is more inconsistent in the literature. Most studies agree that patients with stage IC grade 3, stage IIA with deep myometrial invasion or grade 3 disease, and stage IIB disease have higher risks for recurrence, while patients with stage IA/B grade 3, stage IC grade 1 or 2, or stage IIA grade 1 or 2 without deep myometrial invasion may belong to the intermediate risk group.

Overall, the pelvic recurrence rate for intermediate- to high-risk early-stage disease can be as high as 8% to 25%, but can be reduced to 5% or less with some form

of adjuvant radiotherapy.<sup>9,10,13,14</sup> In fact, some authors concluded that the traditional prognostic factors lose their importance for predicting locoregional recurrence after WPRT.<sup>15,16</sup> Currently, it is difficult to determine whether the addition of vaginal brachytherapy (VB) to WPRT provides further benefit, as there is no randomised trial to address this issue. Review of the literature showed that the improvement in pelvic control after the addition of VB to WPRT is not consistently demonstrated, but an increase in late toxicities frequently occurs (Table 2).<sup>14,17,18</sup>

### Whole Pelvic Radiotherapy

The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) study<sup>19</sup> further confirmed the role of WPRT for pelvic control for patients with intermediate-risk disease.<sup>7</sup> This trial randomised 714 clinically staged patients with stage IB grade 2 or 3 or stage IC grade 1 or 2 disease to receive either adjuvant WPRT 46 Gy over 23 fractions or observation only after surgery. In 2005, the treatment results were updated.<sup>19</sup> A pelvic recurrence rate of 5% was obtained for the WPRT group, which was consistent with the historical findings, and was significantly lower than for the observation group (15%). However, there was no difference in terms of survival, although the overall late complication rate was significantly higher for the WPRT group than for the observation group (2.0% and 0.3%, respectively). This study also confirmed that patients with stage IB grade 2 disease are at low risk and would

**Table 1.** Treatment results for clinically staged early-stage endometrial carcinoma from selected studies.

	Number of patients	Stage	Radiotherapy technique	Pelvic failure rate (vaginal vault failure rate) [%]	Distant failure rate (%)
Carey et al, <sup>10</sup> 1995	384	Low-risk; I	—	2.6 (1.8)	1.3
		High-risk: IC, G3, II, adenocarcinoma	WPRT ± VB	3.2 (2.5)	4.6
Sorbe and Smeds, <sup>11</sup> 1990	404	I	VB alone	1.7 (0.7)	1.2
Alektiar et al, <sup>12</sup> 2002	233	IB G1/2	VB alone	4 (2)	4.0
Weiss et al, <sup>13</sup> 1998	122	Low-risk: IA-IB, G2	± VB	NA (0)	1.3
		High-risk: IC, G3, II	WPRT ± VB	NA (4.5)	2.2

*Abbreviations:* G = histology grade; NA = not available; VB = vaginal brachytherapy; WPRT = whole pelvic external beam radiotherapy.

**Table 2.** Treatment results from selected non-randomised studies comparing whole pelvic external beam radiotherapy plus vaginal brachytherapy with whole pelvic external beam radiotherapy alone for patients with endometrial carcinoma.

	Number of patients	Stage	Radiotherapy technique	Local failure/DFS	Late toxicities after addition of VB
Stryker et al, <sup>14</sup> 1991	86	Clinically staged IBG2-IC	WPRT ± VB	DFS: no difference	Increased
Irwin et al, <sup>17</sup> 1998	550	Clinically staged IC of any grade or any stage I with G3	WPRT ± VB	Local failure: no difference	Increased
Randall et al, <sup>18</sup> 1990	154	Surgically staged I-IV	WPRT ± VB	Local failure: with VB, 2%; without VB, 3.8%	Increased

*Abbreviations:* DFS = disease-free survival; G = histology grade; VB = vaginal brachytherapy; WPRT = whole pelvic external beam radiotherapy.

not gain any additional benefit from WPRT, as the recurrence rate was only 5%, even without WPRT.

The early treatment results of another randomised study also reached the same conclusion.<sup>20</sup> The Medical Research Council — A Study in the Treatment of Endometrial Cancer (MRC-ASTEC) study randomised patients with endometrial carcinoma stage IC or IIA of any grade, stage I with grade 3 disease, or stage I or IIA with poor histology (papillary serous or clear-cell carcinoma) to either adjuvant WPRT 40 to 46 Gy or observation only after surgery.<sup>20</sup> The pelvic initial recurrence rates for the WPRT group and observation group were 4% and 7%, respectively ( $p = 0.038$ ). Although the difference was statistically significant, the magnitude was small. In this study, 29% and 50% of patients in each group also received lymph node dissection and vaginal brachytherapy, respectively, which may dilute the benefit of local control of WPRT. Again, no statistically significant differences in terms of 5-year overall survival (OS), disease-specific survival, and recurrence-free survival were detected. The severe late toxicity for patients in the WPRT group was higher than for those in the observation group (7% and 3%, respectively).

It is disappointing that the benefit offered by WPRT for improvement of pelvic control cannot be translated into any survival gain. Several possible explanations have been postulated. Firstly, many studies included patients with low-risk disease, who may not gain any benefit from WPRT, while the number of patients with high-risk disease may not be large enough to detect any significant survival difference. For example, the PORTEC<sup>7</sup> and the MRC-ASTEC<sup>20</sup> trials enrolled a high proportion of patients with low- to intermediate-risk disease, and intermediate- to high-risk disease, respectively. Therefore, neither study was sufficiently powered to conclude whether or not adjuvant WPRT offers any survival benefit for a subgroup of patients with high-risk disease (stage IC grade 3 and stage IIB). Secondly, WPRT can have a detrimental effect on normal tissue, which could counteract the beneficial effect of disease control. Systemic reviews and meta-analyses may be useful to detect any small but significant survival benefit after WPRT.<sup>20-22</sup> The USA surveillance, epidemiology, and end results population analysis reviewed the records of 2306 patients with stage IC or II endometrial cancer who had received adjuvant WPRT from 1998 to 2003, and compared the results with 1704 patients with disease at a similar stage but

who did not receive WPRT during the same period.<sup>21</sup> This study showed that there was a statistically significant survival difference in favour of patients with stage IC grade 3, stage II grade 2, and grade 3 disease treated with WPRT. For patients surviving more than 5 years, those who had received WPRT plus VB achieved the best 10-year OS. The Cochrane Collaboration meta-analysis included patients from 4 randomised studies, and the results were published in 2007.<sup>22</sup> Although there was a difference in locoregional recurrence in favour of WPRT (absolute reduction of recurrence, 6%; relative risk [RR], 0.28;  $p < 0.00001$ ), this study failed to show any increase in survival for the WPRT group. A subgroup analysis showed that, for patients with stage IC and grade 3 disease, there was a trend towards reduction in deaths from all causes and endometrial cancer after WPRT (RR, 0.76;  $p = 0.24$ ). For patients with either stage IC or grade 3 disease, the benefit of WPRT diminished (RR, 1.00), and for patients with neither of these poor risk factors, the effect of WPRT was detrimental (RR, 1.49). The authors of the MRC-ASTEC study also performed a subsequent meta-analysis that included patients from this study and 2 other randomised studies.<sup>20</sup> The 5-year OS rates for the WPRT and observation groups were 87.8% and 88.0%, respectively, which was not statistically significant. The conclusion was that WPRT was not indicated for the treatment of women with intermediate risk of relapse.

A third possible explanation is that patients with high-risk disease may have already harboured micrometastases during surgery, and WPRT cannot treat the extrapelvic spread. The role of systemic chemotherapy should therefore be further explored, and will be discussed later in this review.

### Observation Alone after Surgery

The fourth possible explanation for the lack of survival benefit of WPRT is the availability of effective local treatment for pelvic recurrence in patients undergoing observation alone.<sup>23</sup> Some authors suggest observation alone after surgery, and consider salvage therapy for any subsequent pelvic recurrence so that patients are not subjected to the potential late WPRT toxicities.<sup>24</sup> However, a subsequent follow-up study of the PORTEC trial showed that the durable salvage rate for the control group was only 48%.<sup>25</sup> In addition, such patients need close follow-up to ensure prompt salvage therapy for any pelvic recurrence. The subsequent toxicities from salvage therapy and the psychological impact of recurrence cannot be overlooked.<sup>23</sup>

Other than observation alone, the results of the MRC-ASTEC study suggest 3 possible ways to achieve a lower pelvic recurrence rate for intermediate- to high-risk patients, but with a lower toxicity: VB alone, lymph node dissection alone, or both VB and lymph node dissection.<sup>20</sup> Other treatment options include new radiotherapy technology such as intensity-modulated radiation therapy to reduce the late toxicity of WPRT<sup>26</sup> and adjuvant systemic chemotherapy to improve extrapelvic control.<sup>27</sup> The former is now considered routine in some centres.<sup>26</sup>

### Adjuvant Vaginal Brachytherapy

VB may be a good substitute for WPRT for intermediate-risk disease, as most recurrences occur at the vaginal vault and the late complication rate for VB is lower than for WPRT.<sup>28</sup> However, there is concern that the risk for regional involvement for patients with high-risk clinically staged disease is so high that VB alone may not be adequate. The data of Aalders et al further support this argument.<sup>29</sup> In this study, 540 patients with clinical stage I disease received VB after surgery and were then further randomised to either WPRT 20 Gy followed by additional parametrial irradiation 20 Gy (VB plus WPRT), or no further WPRT (VB alone). The pelvic recurrence rate was significantly higher for the VB-only group than for the VB plus WPRT group (6.9% and 1.9%, respectively). However, the difference in 5-year survival between the groups was not statistically significant.

An ongoing randomised study — the PORTEC-2 study — should provide definitive answers to this issue for patients with intermediate-risk disease. Patients with intermediate-risk disease, which included stage IIA grade 1 to 2, stage IIA grade 3 with superficial myometrial invasion, or stage IB grade 3 to stage IC grade 1 to 2 and older age, were randomised to either WPRT 46 Gy or VB alone (high-dose rate 21 Gy, medium-dose rate 28 Gy, or low-dose rate 30 Gy). Patients with clinically staged IC grade 3 disease, IIA grade 3 disease and deep myometrial invasion, or stage IIB disease (i.e., high-risk disease) were excluded from this study, as they have a higher regional relapse risk for which VB alone may not provide adequate pelvic control. Until the availability of the results of this study, WPRT should remain the standard adjuvant treatment for patients with clinically staged intermediate-risk and high-risk early-stage disease unless they are physically unfit or have a very high risk for developing late radiotherapy toxicities.

### Lymph Node Dissection (Surgically Staged)

The FIGO surgical staging requires retroperitoneal lymphadenectomy or sampling for complete staging. Many studies have shown that retroperitoneal lymphadenectomy is associated with minimal blood loss and only a small increase in operation time.<sup>30-32</sup> Additionally, retroperitoneal lymphadenectomy could provide more prognostic information, as patients staged surgically were shown to have a better survival rate than those staged clinically.<sup>33,34</sup> The definition of an adequate lymphadenectomy, which includes the extent of lymphadenectomy and the minimal optimal number of lymph nodes harvested, is still not clear.<sup>35</sup> Cragun et al evaluated 509 patients with clinical stage I/IIA disease who underwent pelvic or pelvic plus para-aortic lymphadenectomy.<sup>36</sup> Removal of >11 pelvic nodes in patients with grade 3 histology was associated with significantly better overall survival, while the number of nodes removed and para-aortic lymphadenectomy were not significant predictive factors for patients with grade 1 or 2 disease and the whole group, respectively. In addition, it remains uncertain whether retroperitoneal lymphadenectomy can provide adequate pelvic control, such that WPRT can be omitted.<sup>37,38</sup> The Gynecologic Oncology Group (GOG)-99 study provides useful information to answer this question.<sup>9</sup>

This study randomised 488 patients with surgical stage I disease and with either deep myometrial invasion or grade 3 histology to either WPRT 50.4 Gy or observation only. Even with lymph node dissection, the initial local recurrence rate for the observation group was higher than for the WPRT group (8.9% and 1.6%, respectively). However, most of the pelvic recurrence in the observation group occurred at the vaginal vault only, and recurrence at the pelvic side wall was relatively rare (2.3%). Again, there was no significant difference between the groups in terms of 4-year survival (92% and 86%, respectively;  $p = 0.557$ ).

The late toxicities of combined pelvic lymphadenectomy and WPRT are a concern, particularly severe late gastrointestinal complications and chronic lower limb lymphoedema, although the exact rate of the latter is not frequently mentioned in the literature.<sup>35</sup> A reasonable solution is therefore to add VB after surgical staging, which may offer better vaginal control while sparing most of the late toxicities of WPRT. Retrospective studies show that good pelvic control and survival could be achieved. The commonest reported toxicity for VB is vaginal stenosis, which is more favourable than the toxicity profile of WPRT (Table 3).<sup>39-42</sup>

**Table 3.** Summary of treatment results for adjuvant vaginal brachytherapy for patients with surgically staged early-stage endometrial carcinoma.

	Number of patients	Stage	Adjuvant treatment	Pelvic recurrence (%)	Severe complications (%)
Chadha et al, <sup>39</sup> 1999	159	I	VB alone	0	Vaginal stenosis only
Orr et al, <sup>40</sup> 1997	310	I	± VB	2.5	<3
Horowitz et al, <sup>41</sup> 2002	164	I	VB alone	<1.0	0
Mohan et al, <sup>42</sup> 1998	159	I	VB (6.9% also received WPRT)	4.4	13 (mostly transient leg oedema)

Abbreviations: VB = vaginal brachytherapy; WPRT = whole pelvic external beam radiotherapy.

Many centres, particularly in the USA, now consider VB alone to be the standard therapy for surgically staged patients with intermediate- to high-risk disease, although this approach has never been tested in a randomised study.<sup>26</sup> The Canadian patterns of practice and outcomes study, for example, concluded that WPRT should be considered for high-risk disease (stage IC grade 3), even for patients who are surgically staged, and more clinical trials are warranted to clarify whether or not VB can replace WPRT.<sup>43</sup>

The correct treatment technique for VB should be strictly observed. The treatment length of the upper vagina should be at least 3 to 4 cm, as one study obtained a high recurrence rate at the distal vagina when the treatment length of the irradiated vagina was only 2 cm.<sup>44</sup> A commonly used regimen in many centres in the USA is 7 Gy at 0.5 cm from the surface of a vaginal tandem (high-dose rate remote afterloading), given weekly for 3 fractions. The usual regimen at the Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong, is 5 Gy for 2 fractions per week for 6 fractions. However, the optimal fractionation has not been studied in detail. The

increased risk for vaginal stenosis may be a concern for younger patients, and they should be fully informed of this potential risk. The regular use of vaginal dilators may be considered for such patients.

### Adjuvant Chemotherapy for Intermediate- to High-risk Early-stage Disease

With the recent encouraging results obtained from adjuvant chemotherapy for advanced-stage disease, several studies have been conducted to determine whether adjuvant chemotherapy can provide a survival benefit for intermediate- to high-risk early-stage disease (Table 4).<sup>27,45,46</sup> However, 2 randomised studies have shown that adjuvant chemotherapy alone was not better than WPRT alone.<sup>45,46</sup> An Italian study randomised patients with clinically staged high-risk disease to either chemotherapy alone (cyclophosphamide, adriamycin, and cisplatin) for 5 cycles or WPRT 45 Gy to 50 Gy alone.<sup>45</sup> There was no difference between the groups in 5-year OS and progression-free survival (PFS). Fewer patients in the chemotherapy group could complete the course of treatment than in the WPRT arm (75% and 88%, respectively). Patients treated with chemotherapy

**Table 4.** Randomised studies comparing chemotherapy with or without radiotherapy vs radiotherapy alone for patients with intermediate- to high-risk endometrial carcinoma.

	Number of patients	Stage	Chemotherapy	Radiotherapy	Survival (%)	p Value
Maggi et al, <sup>45</sup> 2006	345	IC G3, III, II G3 with deep myometrial invasion, (excluding PS, CC)	Cyclophosphamide, adriamycin, and cisplatin x 5 cycles	WPRT 45-50 Gy	5-year OS: 69 vs 66	0.770
Susumu et al, <sup>46</sup> 2008	385	IC-IIIc, with deep myometrial invasion	Cyclophosphamide, adriamycin, and cisplatin x ≥3 cycles	WPRT ≥40 Gy	5-year OS: 86.7 vs 85.3	0.268
Nordic Society of Gynecologic Oncology-EC-9501/European Organisation for Research and Treatment of Cancer-55991, <sup>27</sup> 2007	382	I,II, or III (with PPW only or PPLN only); may include PS/CC	Platinum-containing regimen Pre- or post-WPRT x 4 cycles	WPRT ≥44 Gy ± VB	PFS: 79 vs 72	0.030
Radiation Therapy Oncology Group-9905/Gynecologic Oncology Group-194	Pending	IC-IIb, G2 or 3 (excluding PS/CC)	WPRT with concurrent cisplatin x 2 cycles then cisplatin + paclitaxel x 4 cycles	WPRT 50.4 Gy ± VB	Pending	Pending

Abbreviations: CC = clear cell carcinoma; G = histology grade; OS = overall survival; PFS = progression-free survival; PPLN = positive pelvic lymph node; PPW = positive peritoneal washing; PS = papillary serous carcinoma; VB = vaginal brachytherapy; WPRT = whole pelvic external beam radiotherapy.

alone and WPRT alone had a lower distant failure rate and pelvic failure rate, respectively. A Japanese study obtained the same findings for 385 patients with surgically staged IC to IIIC (all with deep myometrial invasion) randomised to either chemotherapy alone (cisplatin, adriamycin, and cyclophosphamide) for  $\geq 3$  cycles or WPRT alone  $\geq 40$  Gy. There were no significant differences between the groups for 5-year OS or PFS.<sup>46</sup> However, subgroup analysis showed that the survival rate for the chemotherapy group was higher in the high- to intermediate-risk group (stage IC older than 70 years, grade 3 disease, or stage II or IIIA). The intrapelvic recurrence rate for the WPRT group was not significantly lower than that for the chemotherapy-alone group, possibly due to the high number of patients who had undergone lymphadenectomy. It is more reasonable to combine both modalities to obtain better pelvic and distant control, particular for patients who are not surgically staged. This approach has recently been confirmed by the early results of a European randomised study.<sup>27</sup> The Nordic Society of Gynecologic Oncology and European Organisation for Research and Treatment of Cancer study, NSGO-EC-9501/EORTC-55991, randomised patients with intermediate- to high-risk disease to either chemotherapy given before or after WPRT for 4 cycles or radiotherapy alone.<sup>27</sup> The treatment protocol required excision of macroscopic lymph nodes only. The investigators could choose adriamycin (or epirubicin) plus cisplatin, carboplatin plus paclitaxel, paclitaxel plus adriamycin plus cisplatin, or paclitaxel plus epirubicin plus carboplatin. The preliminary results showed that treatment with both chemotherapy and radiotherapy was associated with a significant improvement in PFS and disease-specific survival. Further analysis showed that the site with the most significant reduction of progression was in the extrapelvic region. Similar to the Italian study, compliance among the chemotherapy group was a problem, and only 70% of patients completed the course of treatment. In summary, the early results showed that chemotherapy plus radiotherapy, but not chemotherapy alone, may offer a survival benefit for patients with clinically staged intermediate- to high-risk disease, but with the disadvantage of increased toxicities. On the other hand, the Japanese study showed that chemotherapy alone may offer a survival benefit for patients with selected intermediate- to high-risk surgically staged disease. Selection of patients is important to achieve a better therapeutic gain. The optimal chemotherapy regimen has not yet been determined, and different studies have used different designs. The Radiation Therapy Oncology Group-9905 study randomised patients with

stage IC and stage IIA/B grade 2 or 3 disease to receive either concurrent radiotherapy and cisplatin for 2 cycles followed by cisplatin and paclitaxel for 4 cycles or WPRT with or without VB. The recruitment has been completed, and the final results may provide further information on this issue (Table 4).<sup>27,45,46</sup>

## ADVANCED-STAGE DISEASE

### Role of Radiotherapy

Advanced-stage disease is usually defined as stage III or IV, or recurrent disease in most studies. However, this is a very heterogeneous group of patients, in particular, those with stage IIIA disease. Several studies have shown that patients with single extrauterine involvement usually have good treatment outcomes, particularly after adjuvant WPRT.<sup>47-50</sup> Greven et al<sup>47</sup> and Connell et al<sup>48</sup> reviewed the treatment results of patients with stage III disease and stage I to IV disease, respectively, and concluded that multiple extrauterine involvement, but not single extrauterine involvement, was the significant poor prognostic factor. Mariani et al reviewed the treatment results of 51 patients with stage IIIA disease, and concluded that uterine serosal involvement and grade 3 histology were independent predictors of recurrence, but adnexal involvement or positive peritoneal washing were not predictive.<sup>49</sup> A study performed at the Tuen Mun Hospital reviewed 35 patients who had positive peritoneal washing, adnexal involvement, and/or serosal involvement, 94.3% of whom received adjuvant radiotherapy.<sup>50</sup> Among the 28 patients with clinical or pathological negative lymph node involvement, only 2 developed recurrence. Of the other 7 patients who also had positive pelvic and/or para-aortic lymph nodes, 5 developed recurrence and died. In summary, review of the literature shows that adjuvant radiotherapy alone can provide good pelvic control for selected stage III disease, particularly for patients with single extrauterine involvement.

Distant failure (particularly peritoneal metastasis) is an important concern for patients with advanced-stage disease after surgery in addition to local and regional failures. Whole abdominal radiotherapy (WART) is a logical therapeutic option. However, the results are still not conclusive, and the related late toxicities, especially small bowel toxicity, may be a concern.<sup>51,52</sup>

### Chemotherapy for Advanced-stage Disease with Minimal Residual Disease after Surgery

There has been renewed interest in chemotherapy after the results of the recent GOG-122 study were

published.<sup>53</sup> In this study, patients with postoperative FIGO stage III or IV disease and minimal residual disease (<2 cm) were randomised to receive either chemotherapy (adriamycin plus cisplatin) for 8 cycles or whole abdominal irradiation (WART) of 30 Gy plus boost to the pelvic area with or without para-aortic boost of 15 Gy. Patients with lung, liver, inguinal lymph node, or other haematogenous spread were excluded. This study showed that treatment with chemotherapy was associated with a significantly better 5-year PFS (50% vs 38%) and OS (55% vs 42%) than radiotherapy. Similar to other studies, the toxicity rates associated with chemotherapy were high, and the compliance rate was lower than for radiotherapy (63% vs 84%). A planned quality of life analysis showed marked peripheral neuropathy among the chemotherapy group, that was sustained for  $\geq 6$  months.

Although the results of the GOG-122 study are encouraging, there are many unanswered questions. First, it is not certain whether all patients with stage III or IV disease would gain a similar benefit from chemotherapy. As shown in the previous section, stage III disease consists of a heterogeneous group of patients. Selected patients, particularly those with single extrauterine involvement only, could have a sufficiently good prognosis after radiotherapy alone. Secondly, the optimal chemotherapy regimen remains undetermined.<sup>54</sup> The ongoing GOG-209 and GOG-189 studies have been designed to examine the efficacy of the TAP regimen (paclitaxel, adriamycin, cisplatin) and may provide further information on this aspect. Another GOG study, GOG-184, examines the benefit of addition of radiotherapy to chemotherapy. This study randomised patients with stage III or IV disease to either chemotherapy alone (adriamycin and cisplatin) for 6 cycles, or involved field radiotherapy followed by chemotherapy with the same regimen. As chemotherapy has been found to be associated with substantial toxicities in many studies, selection of patients is important, and disease stage, risk factors, and patients' physical fitness should be considered.

### **Hormonal Therapy for Advanced-stage Disease**

Hormonal therapy, in particular progesterone, has been considered as a treatment option for advanced or recurrent disease, with response rates ranging from 15% to 33%.<sup>55</sup> However, in the adjuvant setting, the role of hormonal therapy is still not well defined. Most randomised trials,<sup>56-59</sup> including the large trial by the COSA-NZ-UK

Endometrial Cancer Study Group,<sup>56</sup> could not demonstrate any survival benefit for hormonal therapy when compared with a control treatment. In the only positive study, Urbanski et al recruited patients with better prognostic features to the treatment group, which made interpretation of the results difficult.<sup>59</sup> In addition, progesterone therapy may be associated with an increase in non-endometrial carcinoma-related death due to cardiovascular disease or thromboembolic events. The meta-analysis by Martin-Hirsch et al included 6 randomised studies, and concluded that OS was not improved by adjuvant progestagen and may even have been adversely affected.<sup>60</sup>

### **PAPILLARY SEROUS CARCINOMA**

Uterine papillary serous cancer (UPSC) is an aggressive variant of endometrial carcinoma, which accounts for 3% of endometrial cancers.<sup>61</sup> The survival rates for women with stage I or II UPSC is 35% to 50% and for stage III or IV is 0% to 15%.<sup>62</sup> Extrauterine spread is common in this rare histology type, and is not necessarily predicted by grade and depth of myometrial invasion.<sup>63</sup> Systemic surgical staging is required to identify occult metastasis.<sup>61</sup>

The role of adjuvant therapy for USPC is controversial, as it is difficult to achieve a common consensus given the rarity of this cancer subtype.<sup>61</sup> Many authors agree that adjuvant treatment is not indicated for patients with stage IA disease.<sup>64</sup> Various treatment modalities have been attempted, including WART, systemic chemotherapy, intraperitoneal chemotherapy, and chemoradiotherapy.<sup>65</sup> Given the high risk for extrapelvic spread, even in stage I disease, with a similar behaviour to that of epithelial ovarian cancer, chemotherapy, in particular a platinum-based regimen, has been studied recently.<sup>61,66,67</sup> The large retrospective series reported by Kelly et al reviewed the treatment results of 74 patients with surgical stage I UPSC. This study showed that patients who had received adjuvant platinum-based chemotherapy and vaginal apex radiation achieved the best disease control.<sup>66</sup> However, such an approach for patients with surgical stage I UPSC has not been confirmed by a randomised study. For advanced disease, the most effective management has yet to be determined. One recent GOG study shows that advanced or recurrent USPC was an independent predictor for poorer survival, despite a response to chemotherapy equivalent to the more common endometrioid type of cancer.<sup>68</sup> The GOG-122 study mentioned in the previous section also recruited patients with advanced stage UPSC.<sup>53</sup> This

study suggested that chemotherapy may be a better option than WART.

## CONCLUSIONS

For early-stage low-risk disease (stage IA grade 1 or 2 and stage IB grade 1 or 2), observation only is recommended for most patients. VB may be considered for patients at high risk for local relapse (patients with close margins or lymphovascular invasion). For intermediate-risk disease (stage IA grade 3, stage IB grade 3, stage IC grade 1 or 2, and stage IIA grade 1 or 2 without deep myometrial invasion) to high-risk disease (stage IC grade 3, stage IIA grade 3 or with deep myometrial invasion, and stage IIB any grade), WPRT has traditionally been considered the standard for better locoregional control, but with the disadvantage of an increase in late toxicities. No survival benefit can be demonstrated, even in meta-analyses. There is a hypothesis that VB alone may provide equivalent pelvic control to WPRT for patients with clinically staged intermediate-risk disease. However, until the results of PORTEC-2 are available, WPRT remains a better choice for patients with intermediate-risk disease if lymph node dissection has not been performed. VB alone has been considered to be the standard treatment for patients with intermediate- to high-risk disease by some centres (particularly in the USA), after pelvic and/or para-aortic lymph node involvement has been excluded by lymph node dissection. However, the benefit of this approach has not been confirmed by randomised studies. The early results for adjuvant chemotherapy plus radiotherapy for clinically staged intermediate- to high-risk disease and chemotherapy alone for surgically staged intermediate- to high-risk disease are very encouraging, but with the disadvantage of an increase in toxicity over radiotherapy alone. The optimal chemotherapy regimen has not been determined. Careful selection of patients is important if chemotherapy is considered. Definitive results with longer follow-up are required.

For advanced-stage disease (stage III and IV), several non-randomised studies have shown that — similar to other risk factors — the importance of single-site extrauterine involvement to predict pelvic recurrence diminishes after WPRT.<sup>47-50</sup> For those patients with a poor prognosis (e.g., those with multiple sites of extrauterine involvement, para-aortic lymph node involvement, or gross residual disease after surgery), the risk for extrapelvic recurrence is high. Systemic chemotherapy may be the best choice, and a recent randomised study has confirmed a survival benefit,<sup>53</sup> despite greater toxicities. The optimal regimen and whether or not the addition of

radiotherapy may offer further benefit are yet to be determined. Longer follow-up results for the GOG-122 study<sup>53</sup> and other ongoing trials are required. The role of adjuvant hormonal therapy has not been confirmed by any large randomised study or meta-analysis.

UPSC is a rare but aggressive variant, with a high incidence of extrapelvic involvement, even at an early stage. Comprehensive surgical staging is essential to detect any occult metastasis. Patients with surgically staged IA disease may be observed after surgery. The role of adjuvant chemotherapy with or without radiotherapy for other stages has been studied, but a common consensus has not yet been achieved.

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