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Adjuvant therapy for endometrial cancer

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Endometrial cancer is a common gynecologic malignancy typically diagnosed at early stage and cured with surgery alone. Adjuvant therapy is tailored according to the risk of recurrence, estimated based on the International Federation of Gynecology and Obstetrics (FIGO) stage and other histological factors. The objective of this manuscript is to review the evidence guiding adjuvant therapy for early stage and locally advanced uterine cancer. For patients with early stage disease, minimizing toxicity, while preserving outstanding cure rates remains the major goal. For patients with locally advanced endometrial cancer optimal combined regimens are being defined. Risk stratification based on molecular traits is under development and may aid refine the current risk prediction model and permit personalized approaches for women with endometrial cancer.

Keywords: Adjuvant therapy, Early stage, Endometrial cancer, Locally advanced, Risk stratification

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States and the sixth most common cancer worldwide. In the world, the highest incidence of EC is recorded in North America, followed by Central and Eastern Europe, while the lowest incidence is found in developing countries in Mid- and Western Africa [1]. In the United States approximately 47,000 new cases of uterine cancer and 8,000 related deaths are reported yearly [2]. Based on clinical characteristics that are mirrored by distinct molecular features, two types of uterine cancer are recognized. Type I EC which is more common, representing 80% of cases, is estrogen dependent, and routinely diagnosed at an early stage. Type I EC usually occurs in premenopausal women and has an excellent prognosis. Risk factors include obesity, chronic anovulation such as that induced by polycystic ovary syndrome, exposure to estrogen or tamoxifen, nulliparity, early menarche and late menopause. Type I EC is characterized molecularly by expression of the estrogen receptors (ER) and progesterone receptors, alterations of the PI3K/AKT pathway through activating mutations of the kinases or loss of the phosphatase PTEN, presence of multisatellite instability and β-catenin mutations [3]. Type II EC which is less common, representing up to 20% of all cases, is more aggressive, not driven by estrogen and occurs in thinner and older women, most commonly after menopause [4]. This type includes high grade endometrioid tumors, and the aggressive variant histologic types, serous and clear cell carcinoma. Molecularly, type II EC is characterized by loss of function mutations affecting p53 and p16 and can harbor Her 2/neu amplification [3].

The surgico-pathologic system for staging was introduced in 1988 by the International Federation of Gynecology and Obstetrics (FIGO) and a recent revision was adopted in 2009 (**Table 1**) [5]. The revised staging system intends to provide improved prognostic accuracy relative to the extent of disease, based on refinement of risk stratification models during the past 20 years [5]. The standard surgical staging procedure for EC includes total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), peritoneal washings, and

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Table 1. Comparison between FIGO staging systems 1988 and 2009

Stage	FIGO 1988*	FIGO 2009 [5]
I	a: Tumor limited to endometrium b: Invasion to less than half of myometrium c: Invasion equal to or more than half of myometrium	A: Tumor limited to endometrium or invasion to less than half of myometrium B: Invasion equal to or more than half of myometrium
II	a: Endocervical glandular involvement only b: Cervical stromal invasion	Tumor invades cervical stroma, but does not extend beyond the uterus
III	a: Tumor invades the serosa of the corpus uteri and/or adnexae and/or positive cytological findings b: Vaginal metastasis c: Metastatic to pelvic and/or para-aortic lymph nodes	A: Tumor Invades the serosa and/or adnexae B: Vaginal and/or parametrial involvement C1: Metastasis to pelvic lymph nodes C2: Metastasis to Para-aortic lymph nodes
IV	a: Tumor invasion of bladder and/or bowel mucosa b: Distant metastases, including intra-abdominal metastasis and/or inguinal lymph nodes	A: Tumor invasion of bladder and/or bowel mucosa B: Distant metastases, including intra-abdominal metastasis and/or inguinal lymph nodes

*Adapted after the International Federation of Gynecology and Obstetrics (FIGO) nomenclature, Rio de Janeiro, 1988.

pelvic and para-aortic lymphadenectomy. The routine performance of pelvic and para-aortic lymphadenectomy remains controversial as the procedures adds surgical risks and its therapeutic benefit has not been proven in randomized controlled trials [6]. However the dissection of pelvic and para-aortic lymph nodes provides key prognostic information that critically influences postoperative therapy [7]. Stage remains the most important prognostic factor for EC, early stage patients having the best outcomes and survival decreases with advancing stage. Overall the 5-year survival rates for all grades and histologic subtypes are approximately 78%–90% for stage I, 74% for stage II, 36%–57% for stage III, and 20% for stage IV [8]. In addition to the lymph node status, the tumor histologic type, grade, depth of myometrial invasion, and the presence of lymphovascular invasion are factors used to assess the risk of recurrence and the need for adjuvant treatment [9].

TREATMENT FOR EARLY STAGE ENDOMETRIAL CANCER (STAGES I–II)

Adjuvant therapy for patients with early stage disease is tailored according to the estimated risk of recurrence, which is defined according to FIGO stage and compiled histological factors. Based on retrospective histopathological analyses [10-12] and prospective adjuvant studies for patients with stage I/II EC, three risk groups were characterized: low, intermediate, and high risk. A summary of clinical trials evaluating adjuvant therapy in early stage EC is included in **Table 2** [13-20].

1. Risk stratification for early stage EC

The low risk group includes patients with endometrium-confined disease and well or moderately differentiated tumors. These patients have a very low risk of recurrence and do not require adjuvant treatment. External beam radiation (EBRT) to the pelvis is associated with more risk than benefit and confers no survival advantage. A meta-analysis of 8 studies showed that women younger than 60 years of age who were treated with EBRT had higher risk of developing secondary malignancies (hazard ratio [HR], 2.02; 95% confidence interval [CI], 1.3 to 3.15), higher risk of mortality (HR, 1.36; 95% CI, 1.06 to 1.76) and had experienced lower quality of life from significant radiation toxicity [21]. Therefore, patients in the low risk category do not generally receive adjuvant treatment, but are followed-up carefully during the surveillance period.

The intermediate risk group comprises patients with evidence of myometrial invasion (stage IA/IB) or those with disease extending into the cervical stroma (stage II). The intermediate risk group was further subdivided into low intermediate and high intermediate risk (HIR) groups based on an analysis of patients enrolled in the protocol of the Gynecologic Oncology Group (GOG) 99. The HIR groups was defined according to age and three pathological criteria: histologic grades 2 or 3, presence of lymphovascular invasion and invasion of the outer third of myometrium. The HIR group includes patients older than 70 meeting one of the specified pathological criteria, patients between 50–69 years of age displaying 2 of the 3 pathological criteria and patients younger than 50 years of age fulfilling all three criteria [15]. A benefit from adjuvant EBRT was demonstrated for the HIR group, but not for patients in the low intermediate risk group.

2. Radiation in early stage EC

The effects of adjuvant pelvic radiation (PRT) for the intermediate risk group were studied in several trials, including the Oslo trial, the Postoperative Radiation Therapy for Endometrial

Table 2. Summary of clinical trials investigating adjuvant therapy for early stage EC

Study	No.	Treatment arms	Eligibility	Primary endpoint	Results (%)
Aalders et al. (1968–1974) [13]	540	PRT vs. observation	TAH/BSO followed by Ra-ICRT to vaginal mucosa clinical stage I	LRR, OS	9 yr LRR: 1.9 vs. 6.9 (S) 9 yr OS: 90 vs. 87 (NS)
PORTEC-1 (1990–1997) [14] Long term follow-up (1990–2008)	714	PRT vs. observation	TAH/BSO; All histologies Grade 1 with ≥50% myometrial invasion OR Grade 2 with any invasion OR Grade 3 with <50% myometrial invasion	LRR, OS	5 yr LRR: 4 vs. 14 (p<0.001) 5 yr OS: 81 vs. 85 (NS) 15 yr LRR: 5.8 vs. 15.5 (S) 15 yr OS: 52 vs. 60 (NS)
GOG 99 (1987–1995) [15]	392	PRT vs. observation	TAH/BSO, lymphadenectomy Stage IB, IC, or IIA (occult)	LRR, OS	LRR: 3 vs. 12 4 yr OS: 86 vs. 92 (NS)
PORTEC-2 (2002–2006) [16]	427	PRT vs. VBT	TAH/BSO Age>60 yr and stage 1C grade 1–2 or stage 1B grade 3 OR Stage 2A, any age (excluded grade 3 with >50% myometrial invasion)	LRR	5 yr vaginal relapse: 1.6 vs. 1.8 (NS) 5 yr LRR: 2.1 vs. 5.1 (NS) 5 yr OS: 79.6 vs. 82.7
ASTEC/EN.5 (MRC-NCIC Intergroup trial) (1996–2005) [17]	905	PRT vs. observation VBT allowed	TAH/BSO Stage IA (grade 3), stage IB (grade 3), stage IC, or stage IIA Early stage papillary serous or clear cell of any grade	OS	5 yr LRR: 3.2 vs. 6.1 (NS) 5 yr OS: 83.9 vs. 83.5 (NS)
Sorbe et al. (1997–2008) [18]	527	PRT+VBT vs. VBT	TAH/BSO, node sampling Stage I with 1 of the following risk factors: grade 3, ≥50% myometrial invasion or DNA aneuploidy; negative peritoneal cytology and lymph nodes	LRR, OS	5 yr LRR: 1.5 vs. 5 (S) 5 yr OS: 89 vs. 90 (NS)
JGOG 2033 (1994–2000) [19]	385	PRT vs. CAP	TAH/BSO, pelvic lymphadenectomy Stage IC–IIIC with >50% myometrial invasion	PFS, OS	5 yr PFS: 83.5 vs. 81.8 (NS) HIR: 66 vs. 84 (S) 5 yr OS: 85.3 vs. 86.7 (NS) HIR: 74 vs. 90 (S)
Soderini et al. (1995–2001) [20]	123	PRT vs. observation	Complete surgical staging Stage IB (grade 2–3), stage IC	PFS, OS	OS: 92 vs. 80 (NS) PFS: 88 vs. 79 (NS)

CAP, Cyclophosphamide/Doxorubicin/Cisplatin; EC, endometrial cancer; GOG, Gynecologic Oncology Group; HIR, high intermediate risk group; JGOG, Japanese Gynecologic Oncology Group; LRR, locoregional recurrence; MRC-NCIC, Medical Research Council-National Cancer Institute of Canada; NS, statistically non-significant; OS, overall survival; PFS, progression-free survival; PORTEC, Postoperative Radiation Therapy for Endometrial Cancer; PRT, pelvic external beam radiation therapy; Ra-ICRT, radium intra-cavitary radiotherapy; S, statistically significant; TAH/BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy; VBT, vaginal brachytherapy.

Cancer (PORTEC) 1 trial, protocol GOG 99, and others. The first randomized control trial to show that adjuvant radiation provides locoregional control in early stage EC was published in 1980 by Aalders et al. [13] All patients enrolled in that trial underwent TAH, BSO, but not lymph node dissection. Patients included in the study had stage I disease, all received intracavitary radium and were randomized to either additional PRT or no further treatment. PRT provided better local control compared to observation (1.9% vs. 6.9%; p<0.01), especially in patients with greater than 50% myometrial invasion or grade 3 tumors. However, this did not translate into an improvement in 5-year overall survival [13]. An update of this study was recently reported, confirming that PRT does not improve OS compared to observation (HR, 1.12; 95% CI, 0.95 to 1.33) at a median follow up of 21 years. Interestingly, women younger than 60 who received PRT had decreased survival and an increased risk of subsequent second malignancies (HR, 2.02; 95% CI, 1.3 to 3.15) [22]. The rate of secondary malignancies was as high as 30%, raising concerns regarding the untoward late consequences of radiotherapy. This risk could be attributed in part to the older radiation technology used four decades ago, which delivered higher radiation energy compared to the modern linear accelerators used today. However, late toxicities of radiation should be considered carefully when adjuvant therapy is selected for younger patients.

Subsequent trials (PORTEC 1 and GOG 99) randomized patients

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after surgery to either observation or PRT. Both trials showed significant benefit in locoregional control with adjuvant PRT. In PORTEC 1, the rate of locoregional recurrence (LRR) was 15% for the observation group vs. 4% for the adjuvant PRT group (p<0.001). Similarly in GOG 99, the rate of local recurrence was 12% for the observation group vs. 2% for the adjuvant PRT group (p=0.007). In the HIR subgroup, representing a third of patients enrolled on protocol GOG 99, those randomized to PRT had a lower cumulative incidence of recurrences (26% vs. 6%; HR, 0.42) and overall death rate when compared to the control group (HR, 0.73; 95% CI, 0.43 to 1.26). However, despite a reduction in LRR, both trials failed to show benefit in OS in the general study population. This is partly explained by the high rate of salvage therapy for locally recurrent EC [23-26], by non-EC related mortality, and partly by the overall good prognosis of this patient population. Similarly, a trial of the ASTEC/EN5 groups compared adjuvant PRT to no additional treatment and reported improved local control, but no effect on OS. With a median follow-up of 58 months, OS was 84% in both groups with HR of 1.05 (95% CI, 0.75 to 1.48; p=0.77) [17]. In all studies, adjuvant PRT was associated with significant radiation-related toxicities including diarrhea, fecal leakage, urinary frequency and urgency, which negatively affected quality of life [15,27].

To circumvent adverse effects related to radiotherapy, while not compromising outcomes, a subsequent trial, PORTEC-2 compared vaginal brachytherapy (VBT) to PRT. The primary endpoint of this study was the rate of vaginal recurrence [16]. Similar to PORTEC-1, lymphadenectomy was not required as part of the surgical procedure and patients with high risk disease (stage IC grade 3 and stage II patients) were excluded. At five-years of follow up, there were no significant differences in pelvic recurrence (3.8% in VBT vs. 0.5% in PRT; p=0.02), vaginal recurrence (1.8% in VBT vs. 1.6% in PRT; p=0.74), distant metastasis (8% in VBT vs. 6% in PRT), disease free survival (DFS; 83% in VBT vs. 78% in PRT) and OS (80% in VBT vs. 75% in PRT). Notably, the VBT group suffered significantly lesser toxicities compared to the PRT group. The rate of acute grade 1–2 gastrointestinal (GI) toxicity was significantly lower in the VBT vs. PRT group (12.6% vs. 53.8%). These results support using VBT for patients with patients with HIR early stage EC.

The role of VBT in combination with PRT was compared to VBT alone in patients with intermediate risk EC in a 527 patient randomized trial [18]. Addition of PRT improved locoregional control compared to VBT alone (2.3% vs. 6.8%; p=0.01), but had no impact on survival and was associated with increased acute and late GI and genitourinary toxicity. The results support that combined PRT and VBT should be reserved for patients with high risk disease.

The high risk group is defined as patients with serous or clear cell adenocarcinoma (any stage) or those with high grade and deeply invasive cancer [28]. In an observational study, these patients were treated with EBRT after surgery and compared to the cohort of patients treated on PORTEC-1. The rates of local and distant recurrence were 13% and 31%, respectively, with 30% of patients experiencing EC-related death during the follow up period [28]. These data suggest that this group of patients requires more intensive post-operative treatment and justifies their inclusion in clinical trials incorporating chemotherapy in the adjuvant strategy.

3. The role of chemotherapy in early stage EC

The role of chemotherapy in early stage endometrial cancer has begun to be studied for patients with intermediate and high risk EC. A study from the Japanese Gynecologic Oncology Group (JGOG 2033) included patients with stage IB–IIIC disease and compared PRT alone vs. cisplatin-based chemotherapy (cisplatin, cyclophosphamide, doxorubicin) [19]. The trial of the European Organization for Research and Treatment of Cancer (EORTC 55991) which included stage I–IIIC patients, compared PRT +/− VBT plus cisplatin-based multi-agent chemotherapy vs. PRT +/− VBT [29]. The third study reported by Maggi et al. [30] included patients with high risk early disease (stage IC–II, grade 3 tumors) and compared PRT alone vs cyclophosphamide, adriamycin and cisplatin. All studies showed that the use of chemotherapy lowered the risk of distant metastasis, but did not improve OS in the overall study population. Protocols JGOG 2033 and EORTC 55991 demonstrated an improvement in OS with the use of chemotherapy in the higher risk subgroup defined as either stage II–IIIA or stage IC, grade 3 and/or age >70 (73.6% vs. 89.7%, p=0.006 in JGOG 2033; 75% vs. 82%, p=0.046 in EORTC 55991). A limitation of these studies precluding generalization of results to all patients with early stage EC is that patients with stage III disease or incompletely surgically staged patients were eligible for inclusion and represented 25%–40% of the study population in those trials.

To definitively address whether chemotherapy improves survival in early stage uterine cancer, protocols PORTEC-3 and GOG 249 were designed (**Table 3**). PORTEC-3 randomized patients with high risk early disease (stage I–II, grade 3) and patients with locally advanced disease (stage IIIA–IIIC) to PRT vs. concurrent cisplatin and PRT followed by carboplatin and paclitaxel. GOG 249 randomized early stage HIR patients to PRT vs. VBT followed by three cycles of carboplatin and paclitaxel. The highly anticipated results of these studies will definitively answer whether or not systemic chemotherapy has a place in the management of high risk early stage EC.

Table 3. PORTEC-3 vs. GOG 249 study design

	PORTEC-3	GOG 249
Eligibility criteria	Stage IB and grade 3 and (+) LVSI	Stage I with HIR with (+/−) cytology
	Stage IB serous or clear cell	Stage II any histology
	Stage IC–IIA and grade 3	Stage I–II serous or clear cell and (−) cytology
	Stage IIB–IIIC any histology	
Treatment radomization	Arm-1→PRT (48.6 Gy)*	Arm-1→PRT (4,400 cGy/25 fractions, 5,400 cGY/28 fractions) †
	Arm-2→PRT concurrent with cisplatin followed by carboplatin and paclitaxel ‡	Arm-2→VBT plus carboplatin and paclitaxel §

AUC, area under the curve; GOG, Gynecologic Oncology Group; HIR, high intermediate risk group; LVSI, lymphovascular space invasion; PORTEC, Postoperative Radiation Therapy for Endometrial Cancer; PRT, pelvic external beam radiation therapy; VBT, vaginal brachytherapy.
*Additional VBT boost of 1.8 Gy with cervical invasion. †Additional VBT boost with cervical invasion. ‡Cisplatin 50 mg/m^2 for 2 cycles. Carboplatin 5 AUC and paclitaxel 175 mg/m^2 for 4 cycles. §Carboplatin 6 AUC and paclitaxel 175 mg/m^2 for 3 cycles.

TREATMENT FOR ADVANCED STAGE ENDOMETRIAL CANCER (STAGE III–IVA)

Compared to early stage EC that has an excellent outcome with local therapy, locally advanced uterine cancer (stages III and IVA) represents a heterogeneous group of patients, with increased risk for disease recurrence. This subgroup represents 15% of all cases of EC, but accounts for 50% of EC-related deaths [31]. This patient population's survival is influenced by several factors including: histological subtype, and grade, extent of nodal involvement, and completeness of surgical resection [32-36]. These parameters causing variability in the pool of patients included in clinical studies have led to a wide range of reported five-year survival for this group, spanning between 40% and 80% of anticipated survival [37,38].

The optimal adjuvant treatment strategy for these patients continues to be defined. In the past, surgical resection has been followed by pelvic or whole abdomen radiotherapy. Unfortunately, systemic failures outside the treatment field have limited the impact of radiation on long-term survival. During the past decade, chemotherapy has demonstrated significant activity in patients with locally advanced EC, and now is part of standard treatment. Its benefits rely on the sterilization of systemic foci of metastatic disease and prevention of relapse at distant sites. However, there remains the concern that chemotherapy given alone cannot prevent pelvic recurrences, which ultimately herald systemic relapse. Such pelvic recurrences have been documented as first site of disease relapse in up to 18% of patients with stage III/IVA EC receiving systemic chemotherapy [39]. This observation has provided a strong rationale for continuing to explore combined chemotherapy/radiation strategies for stage III/IVA EC. Development of current adjuvant therapy approaches is described below and the randomized clinical trials addressing management strategies for this patient population are summarized in **Table 4** [11,19,29,30,40,41].

1. The role of radiation therapy in advanced stage EC

Traditionally, radiation therapy has been employed in patients with EC to improve local control after surgery [42]. As previously discussed, the role of radiation was first established in patients with early-stage intermediate and high risk EC [14]. In 1983, Greer and Hamberger [43] published one of the first series of studies applying the concept or radiation treatment for advanced stage uterine cancer. This study showed the feasibility of whole-abdominal irradiation (WAI) followed by pelvic boost, reporting an improvement in survival. Several retrospective case series have also documented an impact of adjuvant radiotherapy in locally advanced disease, but most cohorts of patients were small and non-homogenous. In general, those studies suggested a modest benefit from adjuvant radiotherapy after surgery, with the majority of patients relapsing systemically [44-46]. The results of those studies reiterated the concept that stage III EC should be considered a systemic disease, for which effective systemic therapy is required.

2. Role of chemotherapy in advanced stage EC

The benefits of chemotherapy in patients with EC have been recognized during the past decade. Cisplatin, doxorubicin, and paclitaxel are active agents utilized for the treatment of metastatic or recurrent EC [47-57]. Furthermore, multi-agent chemotherapy emerged as an active therapeutic modality in patients with advanced EC, with response rates (RR) as high as 70% [58]. These observations have formed the basis for testing multi-agent chemotherapy in the advanced EC setting. The GOG studied combination chemotherapy in protocols GOG 107 (doxorubicin plus cisplatin [AP] vs. doxorubicin alone) and

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Table 4. Randomized trials investigating adjuvant treatment in high risk/advanced stage EC

Study	No. of patients	Eligibility	Adjuvant treatment arms	Primary endpoint	Outcome (%)
Morrow et al. (GOG 34; 1977–1986) [11]	181	Stage I and II (occult) with high risk features	PRT vs. PRT+CT(A)	OS, PFS	No difference between groups
Maggi et al. (1990–1997) [30]	340	Stage I–III (high risk profile) Serous/clear cell histology excluded	PRT vs. PRT+CT(CAP)	OS, PFS	5 yr PFS: 63 vs. 63 (NS) 5 yr OS: 69 vs. 66 (NS)
Kuoppala et al. (1992–1996) [40]	156	Stage IA–B G3, IC–IIIA	PRT vs. PRT+CT(CEP)	DSS, PFS	5 yr PFS: 82 vs. 77 (NS) 5 yr DSS: 85 vs. 82 (NS)
GOG 122 (1992–2000)	396	Optimally debulked Stage III–IV	WAI vs. PRT+CT(CD)	PFS	5 yr PFS: 38 vs. 42 (p<0.01) 5 yr OS: 42 vs. 53 (p<0.01)
JGOG 2033 (1994–2000) [19]	385	Stage IC–IIIC with >50% myometrial invasion	PRT vs. CT(CAP)	PFS, OS	5 yr PFS: 84 vs. 82 (NS) HIR: 66 vs. 84 (p=0.024) 5 yr OS: 85 vs. 87 (NS) HIR: 74 vs. 90 (p=0.006)
NSGO/EORTC (1996–2007) [29]	383	Stage I–III (high risk profile)	PRT vs. PRT+CT(M)	PFS	5 yr PFS: 72 vs. 79 (p=0.04) 5 yr OS: 76 vs. 83 (NS)
MaNGO ILIADE-3 (1998–2007) [29]	157	Stage IIB–IIIC Serous/clear cell histology excluded	PRT vs. PRT+CT(CD)	PFS	5 yr PFS: 61 vs. 74 (NS) 5 yr OS: 73 vs. 78 (NS)
GOG 184 (2000–2004) [41]	552	Optimally debulked Stage III–IV	VD-RT+CD vs. VD-RT+CDP	RFS	3 yr PFS: 62 vs. 64 (NS)
GOG 258 (2009–present)	804	Optimally debulked Stage III–IVa Stage I–II disease-serous or clear cell histology	VD-RT/cisplatin+CP (4 cycles) vs. CP (6 cycles)	RFS	Ongoing study
PORTEC III (2006–present)		Stage I–III (high risk profile)	PRT vs. PRT/cisplatin+CP (4 cycles)	OS, FFS	Ongoing study

A, doxorubicin; CAP, cyclophosphamid/doxorubicin/cisplatin; CD, cisplatin/doxorubicin; CDP, cisplatin/doxorubicin/paclitaxel; CEP, cyclophosphamide/epirubicin/cisplatin; CP, carboplatin/paclitaxe; CT, chemotherapy; DSS, disease specific survival; EC, endometrial cancer; EORTC, European Organisation for Research and Treatment of Cancer; FFS, failure-free survival; GOG, Gynecologic Oncology Group; HIR, high intermediate risk group; JGOG, Japanese Gynecologic Oncology Group; M, multiple chemotherapy regimens; NS, statistically non-significant; NSGO, Nordic Society of Gynaecological Oncology, OS, overall survival; PFS, progression-free survival; PORTEC, Postoperative Radiation Therapy for Endometrial Cancer; PRT, pelvic external beam radiation therapy; RFS, recurrence free survival; VD-RT, volume directed radiation therapy; WAI, whole abdominal irradiation.

GOG 163 (AP vs. cisplatin plus paclitaxel). In both protocols, the overall RR to AP was at least 40%, with complete responses observed in approximately 20% of patients [58]. The toxicity profile of the combination arm was considered acceptable.

The first study to compare systemic chemotherapy to radiotherapy in women with stage III/IVA optimally debulked EC was GOG 122 [39], a randomized comparison between WAI and combination chemotherapy (AP). With a median 74 months follow-up, the hazard ratio for PFS (HR, 0.71) and OS (HR, 0.68) favored the chemotherapy arm. This trial set a new standard for patients with locally advanced EC, bringing systemic chemotherapy to the forefront of EC management. However 18% of patients treated on the AP arm developed pelvic recurrence as the first site of relapse, which suggested that despite improved systemic control compared to WAI, local control remains insufficient [39]. Other retrospective analyses have also indicated that patients treated with systemic chemotherapy alone experience a considerable rate of pelvic recurrences up to 20%–30% [59,60]. These observations have provided the rationale for a combined chemotherapy/radiotherapy approach, as discussed in section IIIC.

To further improve the results of systemic chemotherapy and improve systemic disease control, a triple agent regimen was designed, including three agents with known activity in EC. The regimen was first tested in the metastatic or recurrent EC setting in protocol GOG 177, which compared AP to the triplet doxorubicin/cisplatin/paclitaxel (TAP) [61]. The triplet was more active, with RR of 57% for TAP (22% complete

response [CR], 35% partial response [PR]) vs. 34% for AP (7% CR, 26% PR; p<0.001). The HR for progression or death for TAP relative to AP was 0.60 (95% CI, 0.46 to 0.78; p<0.001). This translated into a median progression-free survival (PFS) of 8.3 for TAP vs. 5.3 months for AP, and a median OS of 15.3 months for TAP vs. 12.3 months for AP (p=0.037) [61]. However, the toxicity of the regimen was high and growth factor support was mandatory. Up to 39% of patients developed greater than grade 1 neuropathy.

When the TAP regimen was applied to the adjuvant setting, following tumor volume-directed radiotherapy in stage III–IVA endometrial cancer (GOG 184), and compared to the doublet AP, no difference in recurrence free survival was noted at 36 months [41]. Further, the crude proportion of patients with acute grade 3–4 GI toxicity was 13% in the AP arm and 18.3% in the TAP arm. Protocol therapy was discontinued in 14% of patients randomized to TAP due to toxicity and in an additional 4.6% due to patient refusal. The crude proportion of patients with late grade 3–4 GI toxicity, including bowel obstruction and fistula, in both doxorubicin containing regimens was 6%–8%. These results suggested that TAP although highly active in the metastatic setting, is not superior to the doublet regimen omitting paclitaxel and is too toxic to be administered routinely after tumor volume directed radiotherapy in the adjuvant setting.

These considerations led to a well justified interest in developing a less toxic regimen for this patient population. This objective was addressed by protocol GOG 209, designed to compare the commonly used and popular regimen carboplatin/paclitaxel (CT) to the triplet TAP. The CT regimen had been tested in several phase II studies, with encouraging preliminary results [62,63]. Hoskins et al. [62] reported a 78% RR in patients with advanced non-serous endometrial cancer, and a RR of 51% in patients with serous papillary uterine cancer. The three-year survival for patients with advanced non-serous papillary endometrial cancer was 62%, whereas patients with advanced papillary serous endometrial carcinoma treated with CT had a probability of 39% three-year OS. Similarly, Nakamura et al. [63] reported a complete RR to CT of 45.5% in metastatic EC and Price et al. [64] reported a RR of 63% in their series of 20 patients. Lastly, a randomized phase II trial suggested that the CT combination is at least as active as AP, with RR of 44% (CT) vs. 26% (AP) [65]. When compared in a randomized fashion in GOG protocol 209, CT was found to be not inferior to TAP in terms of PFS and OS. At the reported interim analysis, the median PFS was 14 months in both arms (HR, 1.03), while median OS was 32 months vs. 38 months in patients treated with CT vs. TAP (not significant, HR, 1.01). Additionally, CT was better tolerated than TAP [66]. Specifically, the incidence of grade >1 sensory neuropathy for patients receiving TAP was 26% compared with 19% in those receiving CT (p<0.01). Common grade >2 toxicities more often (p<0.01) reported with TAP vs. CT included: thrombocytopenia (23% vs. 12%), other hematologic (30% vs. 22%), vomiting (7% vs. 4%), diarrhea (6% vs. 2%), and metabolic (14% vs. 8%); whereas neutropenia (52% vs. 79%) was more often reported with CT. Study treatment was discontinued due to toxicity in 18% of patients on TAP and in 12% of patients randomized to CT. The 7 planned cycles were completed in 62% of those on TAP and 69% on TC (p=0.01). At the conclusion of these studies AP, TAP, and CT appear to be active regimens in advanced EC; however the CT regimen is better tolerated and accepted in the community.

3. Role of combined chemotherapy and radiation therapy in locally advanced EC

Based on these considerations, it is compelling to hypothesize that a strategy combining chemotherapy and radiotherapy would yield better results in this patient population by controlling both systemic and local recurrences. It is important to note that 30% of patients included in GOG-122 treated with systemic chemotherapy recurred in the pelvis and in the abdomen. This observation suggested that patients treated with systemic chemotherapy experience a finite rate of local failure, which could contribute to compromise in overall survival. This concern supported including tumor volume-directed radiotherapy in the upfront approach of stage III/IVA EC, with the intent of preventing local recurrences. Whether this improved local control translates into an improvement in OS remains unproven.

Several small studies have suggested that combination chemo and radiotherapy induce better outcomes. Onda et al. [67] reported that among 30 patients with Stage IIIC endometrial cancer treated with combination WAI and chemotherapy, the five-year OS was 84%. A study reported by Bruzzone et al. [68] noted PFS of 30% and OS of 53% among 45 poor-prognosis stages III and IV uterine cancer treated with pelvic radiotherapy and chemotherapy including cisplatin, epidoxorubicin and cyclophosphamide. Hogberg et al. [29] also showed that combination chemoradiation is superior to radiation alone with a 36% reduction in the risk for relapse or death (HR, 0.64; 95% CI, 0.41 to 0.99; p=0.04). The phase II trial run by the Radiation Therapy Oncology Group (protocol 9708) demonstrated feasibility and high efficacy of combined chemoradiation approach in patients with EC at high risk of recurrence [69]. The regimen studied involved cisplatin given together with PRT (45 Gy) followed by four cycles of cisplatin and paclitaxel. At four years, the cumulative proportions of patients with pelvic, regional and distant recurrence were

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2%, 2%, and 19%, respectively. The percent of patients alive or alive and disease free at 4 years were 85% and 81%, respectively. For stage III patients, four-year OS and DFS was 77% and 72%, respectively. Another Italian pilot study used paclitaxel with EBRT in high risk patients with EC, demonstrating tolerability of the approach [70]. The combined modality approach has demonstrated efficacy and feasibility in many other tumor types [71-74] including cervical cancer [75-78]. Those compelling results suggested the feasibility of this approach and supported studying it further in larger trials.

An initial evaluation of systemic chemotherapy and volume directed radiotherapy in GOG protocol 184 showed that the combined approach yielded a three-year DFS of 62%–64% in this setting. In this protocol, women with optimally debulked stage III and IVA endometrial cancer were randomized to pelvic radiotherapy followed by systemic chemotherapy. The two arms of the trial compared outcomes between TAP vs. AP chemotherapy, the primary endpoint being DFS. There was no statistically significant difference in DFS with the addition of paclitaxel to the AP regimen, but TAP after radiotherapy had a more unfavorable toxicity profile [41], as previously discussed.

The ongoing international protocol GOG 258 compares tumor volume-directed radiotherapy administered concurrently with cisplatin and followed by 4 cycles of CT against CT chemotherapy alone. It has been hypothesized that administration of upfront concurrent chemotherapy and radiation would have advantages including synergistic anti-tumor activity from the combined approach [72,73] and circumvention of possible systemic relapses during the delay imposed by delivery of radiotherapy. The excellent track record and experience with this approach from the cervical cancer studies [76-79] further supported the strategy. It is anticipated that protocol GOG 258 will answer critical questions regarding the impact of chemo-radiation on OS, the tolerability of the approach, and the short- and long-term impact on the quality of life. If positive, the combined chemo-radiotherapy approach would become a new standard that could easily be adopted in the community practice and used as a backbone for treatments incorporating molecularly driven therapies.

MOLECULAR BIOMARKERS IN ENDOMETRIAL CANCER AND IMPLICATIONS ON MANAGEMENT

While traditional methods of surgical staging and tumor histopathology are the basic criteria for risk stratification in EC, it is clear that they remain insufficient, as despite optimal risk-adapted treatment, some patients classified as low risk recur, while other patients classified as high risk may be over treated [79]. In recent years it has been hypothesized that molecular methods for outcome prediction may aid optimal distinction of risk groups [80]. Several promising molecular prognostic factors are described below.

The cancer genome atlas (The Cancer Genome Atlas, TCGA) research network performed an integrated genomic, transcriptomic, and proteomic analysis of endometrial carcinomas [81]. Based on the molecular alterations identified, EC were categorized into 4 subgroups (**Table 5**), which independently predicted clinical outcomes. Specific signaling pathway alterations were associated with each subgroup. Interestingly, 25% of high grade endometrioid tumors harbored serous-like molecular alterations associated with correspondingly aggressive clinical behavior. These observations suggested that patients with serous-like endometrioid tumors might benefit from more intensive treatment similar to that applied to serous endometrial carcinoma. Pasthan and collaborators

Table 5. Risk stratification based on molecular characteristics identified in the TCGA analysis

Group	POLE ultramutated	MSI hypermutated	Copy-number low	Copy-number high
Histology	Primarily endometrioid histology			Most serous/mixed histology tumors and 25% of grade 3 endometrioid tumors
Group identity	POLE exosome domain mutation (100%)	MSI (*MLH1* gene hypermethylation)	Low SCNAs	High SCNAs
Characteristic	Low SCNAs	Low SCNAs	High frequency CTNNB1, SOX17, KRAS, β-catenin mutations	High frequency TP53, ERBB2, CDKN2A mutations and low PTEN expression
	High mutation rate (232×10^{-6}/Mb)	High mutation rate (18×10^{-6}/Mb)	Low mutation rate (2.9×10^{-6}/Mb)	Low mutation rate (2.3×10^{-6}/Mb)
Outcome	Better OS and PFS			Poor OS and PFS

MSI, microsatellite instability; OS, overall survival; PFS, progression-free survival; POLE, catalytic subunit of DNA polymerase epsilon; SCNA, somatic copy number alteration; TCGA, The Cancer Genome Atlas.

conducted further analyses of the TCGA-EC data [82], correlating molecular alterations to clinical outcomes in patients with early stage disease. He described DNA copy number alterations (CNA) as a prognostic indicator in EC, independently of standard histopathology and stage of the disease. Subtypes with 1q amplification and serous-like CNA had the worst outcome. Surprisingly, patients with endometrioid 1q amplification had worse outcomes than the serous-like group. If confirmed, these findings suggest that these subgroups of patients should be considered for more aggressive adjuvant therapy. In contrast to this, patient with polymerase epsilon, catalytic subunit (POLE) mutations seem to have excellent outcomes with minimal risk of recurrence [83-85].

The importance of other molecular markers as prognostic indicators for EC has also been described. Several key signaling-pathway alterations including the PI3K/PTEN/AKT/mTOR, FGF/FGFR, WNT/CTNNB1, and TGF-β pathways have been described and their prognostic significance is being tested and validated [79,86]. A recent report identified the expression of L1 cell adhesion molecule (L1CAM) in stage I endometriod tumors [87]. L1CAM positive cancers had very high likelihood of recurrence (HR, 16) and death (HR, 15), suggesting that this subgroup of tumors should be considered for adjusted therapy. Loss of estrogen receptor-α expression was found to be associated with markers of epithelial-mesenchymal transition and correlated clinically with poor prognosis [86], suggesting that this commonly assessed biomarker in EC should be taken into account in risk prediction models. Various other biomarkers including p53 overexpression, high levels of phosphorylated stathmin (S38) expression, ERBB2 overexpression, aneuploidy, and lipocalin 2 have been described in association with aggressive tumors and appear to impact the survival of women with EC [88].

In conclusion, these recent discoveries provide new opportunities for improved risk stratification and provide opportunities for exploring new targeted therapy in EC. However, standardized testing and further evaluation in prospective trials is needed to validate the proposed markers. We anticipate that future risk stratification models will take into account not only histological and surgical characteristics, but also unique and distinctive molecular markers reflecting the intrinsic biology of the tumor, to enable a truly personalized approach for EC.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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