10

Adjuvant Chemotherapy for Endometrial Cancer

N. Susumu[1], H. Nomura[1], W. Yamagami[1], A. Hirasawa[1],
K. Banno[1], H. Tsuda[1], S. Sagae[2] and D. Aoki[1]
[1]School of Medicine, Keio University, Shinjyuku-ku, Tokyo
[2]JR Sapporo Hospital, Sapporo, Hokkaido
Japan

1. Introduction

The prognosis of early-stage endometrial cancer is favorable, even when treated using surgery alone, whereas recurrent cases or advanced cases (stage III or IV) with progression beyond the uterus have a poor prognosis[1], and therapy for such cancers is still in the exploratory stages. Stage I and II cases are sometimes treated with adjuvant therapy to prevent recurrence after surgical therapy; however, the treatment options for these cases remain controversial. The boundaries encompassing intermediate risk cases may be approached in several ways, and it would be difficult to say that any consensus has been reached, although examples often include stage IIB (FIGO stage 1988) and higher, stage IC endometrioid adenocarcinoma, all grade 3 (poorly-differentiated) endometrioid adenocarcinoma, non-endometrioid adenocarcinoma, and marked lymphovascular space invasion[2,3]. Radiation therapy and chemotherapy are the two primary modalities of postoperative adjuvant therapy for patients with these types of endometrial cancer characterized by a poor prognosis or a risk of recurrence. In this chapter, we first refer briefly to adjuvant radiotherapy.

2. Radiation therapy for endometrial cancer

In Europe and the US, the postoperative therapy most commonly used for intermediate-risk patients with advanced endometrial cancer or early-stage cancer who are at risk of recurrence is mainly radiation therapy[4]. In Japan, on the other hand, chemotherapy is often chosen as a postoperative therapy, and radiation therapy is performed only for limited cases. Radiation therapy is indicated as an option for initial treatment only when surgery would be difficult to perform from a practical perspective, such as in advanced cases that are considered inoperable, and in cases where surgery is considered a high-risk procedure because of serious complications, obesity, or other reasons[5]. The following types of radiation therapy can be used for endometrial cancer following a hysterectomy. (1)Vaginal brachytherapy: A radioactive source for brachytherapy is inserted into the vagina and left there for two to three days. (2)External-beam radiation therapy (EBRT): Tumors are exposed to radiation from outside the body.

There are two kinds of EBRT: whole abdominal irradiation (WAI) and whole pelvic irradiation (WPI). WAI or WPI is usually carried out as postoperative radiation therapy and is sometimes accompanied by vaginal brachytherapy.

The effects of postoperative radiation therapy on intermediate-risk cases of early-stage endometrial cancer have been studied in comparison with groups observed over time in the absence of postoperative treatment in NRH[6], PORTEC[7], GOG-99[8]. Although these reports are from different regions, they all showed the same results. Specifically, the effect in suppressing local recurrence was significantly better in the radiation therapy groups, but radiation did not significantly prolong progression-free survival (PFS) or overall survival (OS).

A study on the effects of postoperative (adjuvant) EBRT on outcome in patients with early-stage endometrial cancer was recently reported in The Lancet[9]. Out of 905 patients with early-stage cancer in seven countries that had been enrolled in the ASTEC and EN.5 studies, intermediate to high-risk patients who had undergone surgery for endometrial cancer were randomly assigned to an observation or an EBRT group. The risk of developing distant metastasis based on the PORTEC and GOG99 data, where a high risk was defined as "all papillary serous and clear cell subtypes, all other subtypes in IC (grade 3) and IIA (grade 3), and all patients with stage IIB", and intermediate risk was defined as "subtypes other than papillary serous and clear cell histology within stage IA and IB (grade 3) and stage IC and IIA (grades 1 and 2)." The results of an analysis revealed that, after 58 months of follow up, the hazard ratio (HR) for death was 1.05 (95% CI, 0.75 to 1.48; $P = 0.77$) in 68 out of 453 subjects in the group observed over time and in 67 out of 452 subjects in the EBRT group, indicating no difference in OS. There was also no significant difference in terms of recurrence-free survival (RFS), with a HR of 0.93 (95% CI, 0.66 to 1.31; $P = 0.68$). The incidence of distant recurrence was also the same (8% in the observation group and 9% in the EBRT group), but the HR of 0.46 (95% CI, 0.24 to 0.89; $P = 0.02$) for vaginal or pelvic initial recurrence indicated that local recurrence was suppressed in the EBRT group. However, since these numbers do not include cases of distant metastasis or simultaneous local recurrence/distant metastasis, which account for 65% of recurrences, the overall outcome was not considered to have improved. The development of acute toxicity was also higher in the EBRT group, with a rate of 43% compared to the rate of 27% in the group without radiation therapy.

A meta-analysis[9] of 2011 cases comprising the PORTEC and GOG99 data was performed in addition to the above ASTEC and EN.5 data. The HR for OS was 1.04 (95% CI, 0.84 to 1.29; $P = 0.38$), indicating no significant differences depending on whether or not adjuvant EBRT was performed. A sub-analysis divided the patients into what the authors termed intermediate risk and high risk also revealed no significant differences in OS between the ASTEC+EN.5 and the ASTEC+EN.5+PORTEC+GOG99 data.

Because adjuvant EBRT thus failed to improve survival and also resulted in adverse effects in early-stage endometrial cancer patients who had a risk of recurrence, the authors concluded that such treatment could not be recommended for patients with early-stage endometrial cancer.

3. Chemotherapy for advanced or recurrent endometrial cancer

Although adjuvant EBRT can be expected to be effective to a certain extent for advanced or recurrent endometrial cancer, chemotherapy with anti-tumor agents is also being additionally performed in Europe and the US. After many changes in regimens, AP therapy

(combining doxorubicin and cisplatin) is currently the standard therapy. The changes in regimens are summarized below.

From the 1970s to the 1980s, doxorubicin monotherapy was reported to result in a response rate of 20% to 42%[10], and a good response rate of 45% to 60% was reported in a subsequent phase II study combining cisplatin with doxorubicin[11]. These two drugs therefore came to be positioned as key drugs in chemotherapy for endometrial cancer. In the 1990s, the Gynecologic Oncology Group (GOG) in the US and the European Organization for Research and Treatment of Cancer (EORTC) conducted phase III randomized comparative studies on "doxorubicin vs. doxorubicin + cisplatin (AP therapy)" in both the GOG107[12] and EORTC55872[13] trials, respectively, and the response rates of 25% vs. 42% in the GOG107 study and 43% vs. 17% in the EORTC55872 study demonstrated the efficacy of AP therapy. Although no significant differences in OS were found in the GOG-107 study, AP therapy was shown to be superior in the EORTC55872 study. On the other hand, CAP (cyclophosphamide + doxorubicin + cisplatin) therapy is also being used for endometrial cancer in Japan, where chemotherapy is more often performed as a postoperative therapy[5]. However, cyclophosphamide was not found to result in significant differences in the response rate in phase II studies of CAP therapy and AP therapy[14], while the GOG48 study on "doxorubicin vs. doxorubicin + cyclophosphamide (AC therapy)" also revealed no significant differences in the response rate, response period, or OS, thus contradicting the usefulness of concomitant cyclophosphamide for endometrial cancer[15];AP therapy has come to be acknowledged as the standard chemotherapy for endometrial cancer in Japan as well.

Radiation therapy and chemotherapy are thus the primary modalities of therapy that should be used after surgery for endometrial cancer. However, the following three questions still need to be answered:

1. Which is more effective for advanced or recurrent cancer: radiation therapy or chemotherapy?
2. Radiation therapy has been shown to be ineffective for early-stage patients classified as being at risk for recurrence, but is chemotherapy effective?
3. Alternatively, is the combination of radiation therapy and chemotherapy effective for early-stage patients classified as being at risk for recurrence?

4. Radiation therapy vs. chemotherapy as adjuvant therapy for endometrial cancer

Three randomized studies have compared radiation therapy and chemotherapy as adjuvant therapies for endometrial cancer (Table 1).

4.1 GOG122

The GOG122[16], reported in the US in 2006, was a randomized study comparing WAI and AP therapy as first-line therapies for stage III and IV cases with residual tumors no greater than 2 cm after surgery. The HR for progression adjusted for stage was 0.71, favoring AP therapy (95% CI, 0.55 to 0.91; $P < 0.01$). At 60 months, 50% of the patients receiving AP were predicted to be alive and disease-free after adjustments for stage, compared with 38% of patients receiving WAI. The stage-adjusted death HR was 0.68 (95% CI, 0.52 to 0.89; $P < 0.01$), favoring AP therapy. Moreover, at 60 months and after adjustments for stage, 55% of the AP patients were predicted to be alive, compared with 42% of the WAI patients. The PFS and OS were both significantly higher in the AP arm, but greater acute toxicity was seen in the

study	phase	year	eligibility	treatment arm	number of cases	compliance rate (%)	percentage of stage I/II/III/IV	percentage of PLN	percentage of PAN	percentage of G3 or serous/clear cell	5-year PFS (%)	5-year OS (%)	hazard ratio (HR) (95%CI)	adverse effects
GOG122 (Randall et al.)	III	2006	stage III and IV cases with residual tumors no greater than 2 cm after surgery	AP(60/50)X7 + P(50)X1, q3w (A: maximum 420 in total)	194	63					42[a]	53[a]	HR of PFS (CT vs. RT): 0.71 (0.55-0.91), HR of OS (CT vs. RT) : 0.68 (0.52-0.89)	hematologic G3/4: 88% (CT) vs. 14% (RT), GI G3/G4: 20% vs. 13%, neurotoxicity 7% vs. <1%, deaths related to Tx: 4% vs. 2%
				WAI + boost EBRT (pelvis +extended field) (45Gy)	202	84	0/0/73/27	87	75	52 (serous+clear+ undifferentiated : 26)	38	42		
Italian study (Maggi et al.)	III	2006	stage IC G3, stage II A to IIB G3 with more than 50% myometrial invasion, stage III disease with no gross residual tumor	CAP(600/45/50) X5, q4w	174	75					63	66	HR of PFS (RT vs. CT): 0.92 (0.65-1.30), HR of OS (RT vs. CT): 0.85 (0.72-1.50)	neutropenia G3/4: 35%, radiation proctitis G3: 4%, diarrhea G3: 16%
				EBRT (pelvis ± extended field) 45-50Gy	166	88	26/9/65/0	NA	NA	56 (serous+clear+ undifferentiated : 0)	63	69		
JGOG2033 (Susumu et al.)	III	2008	stage IC–IIIC with deeper than 50% myometrial invasion, and with no residual tumor:	CAP(333/40/50) X3 or more, q4w	193	97					82	87	HR of PFS (CT vs. RT) : 1.07 (0.65-1.76), HR of OS (CT vs. RT) : 0.72 (0.40-1.29)	G3/4 toxicities: 5% (CT) vs. 2% (RT), treatment-related death: 0%
				EBRT (pelvis ± extended field) 45-50Gy	192	99	61/14/25/0	96	29	14 (serous+clear+ undifferentiated : 0)	84	85		
JGOG2033 (subset analysis: high-intermediate risk)					64						84[a]	90[a]	HR of PFS (CT vs. RT) : 0.44 (0.20-0.97), HR of OS (CT vs. RT) : 0.24 (0.09-0.69)	
					56						66	74		

a: significantly better

Table 1. Randomized trials comparing radiation therapy and chemotherapy as an adjuvant therapy for endometrial cancer.

AP arm. Treatment probably contributed to the deaths of 8 patients (4%) in the AP arm and 5 patients (2%) in the WAI arm, indicating that AP therapy was associated with a somewhat stronger toxicity. However, in view of the survival data, AP chemotherapy appeared to be better than radiation therapy as a first-line postoperative therapy for advanced endometrial cancer. This was the first trial to reveal the positive effects of chemotherapy over radiation therapy. A subgroup analysis revealed that significantly lower HRs regarding OS were recognized in patients younger than 60 years old, cases with microscopic residual tumors, cases with a pathological subtype of endometrioid adenocarcinoma, and stage III cases. After the results of this study were reported, chemotherapy tended to be more often incorporated into adjuvant therapy for endometrial cancer.

4.2 Italian study

Maggi R et al. [17] reported a multicenter randomized trial comparing five courses of adjuvant chemotherapy with CAP (cyclophosphamide, 600 mg/m^2; doxorubicin, 45 mg/m^2; and cisplatin, 50 mg/m^2) and external radiation therapy (45 Gy) for mainly high-risk endometrial cancer patients, including stage IC grade 3, stage IIA to IIB grade 3 with more than 50% myometrial invasion (stage I/II: 36%), and also stage III disease. The pathological subtype was restricted to endometrioid type. Selective pelvic and paraaortic node sampling were performed; however, the percentage of patients undergoing a lymphadenectomy was not stated. More than 60% of the cases were stage III and had a high risk of recurrence. The 3-, 5-, and 7-year OS rates were 78%, 69% and 62% in the RT group and 76%, 66% and 62% in the CT group. The 3-, 5-, and 7-year PFS rates were 69%, 63%, and 56% and 68%, 63%, and 60%, respectively. This study revealed no significant differences in the OS or the PFS. Radiation therapy delayed local relapses, and CT delayed distant metastases.

4.3 JGOG2033

In 2008, the Japanese Gynecologic Oncology Group (JGOG) published a paper[18] about a randomized phase III trial (JGOG2033) comparing adjuvant chemotherapy with cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (50 mg/m^2) (CAP) administered every four weeks for three or more cycles with radiotherapy administered using pelvic EBRT (PRT) at 50 Gy in 385 patients with endometrioid adenocarcinoma and myometrial invasion deeper than 50%, myometrial invasion, most of whom had an intermediate -risk but a small proportion of whom had a high -risk of recurrence after the initial operation for endometrial cancer. No statistically significant differences in the PFS or OS were recognized between the patient groups treated with the two modalities. However, in the high intermediate-risk (HIR) group consisting of (1) patients with stage IC disease who were over 70 years of age and/or had G3 endometrioid adenocarcinoma and (2) patients with stage II or IIIA disease (positive cytology), the CAP treatment was associated with a significantly higher PFS rate (83.8% vs. 66.2%) as well as a higher OS rate (89.7% vs. 73.6%). Adjuvant chemotherapy was emphasized as being a useful alternative to radiotherapy for patients with intermediate-risk endometrial cancer.

In this study, a pelvic lymphadenectomy was performed in 96% of the cases and a paraaortic lymphadenectomy was performed in 29% of the cases; furthermore, the ratio of stage I or II cases was higher (75% vs. 35%) and the ratio of grade 3 tumors was lower (14% vs. 56%). Most of the cases in JGOG2033 study had an intermediate risk, while most of the cases in the Italian study[17] had a high risk. Although both of these studies used the CAP regimen, the doses of cyclophosphamide and doxorubicin were lower and the number of chemotherapy cycles was fewer in the JGOG2033 study (Table 2). In fact, the incidence of

study	phase	year	eligibility	treatment arm	number of cases	compliance rate (%)	percentage of stage I/II/III/IV	percentage of PLN	percentage of PAN	percentage of G3 or serous/clear cell	5-year PFS (%) 5-year OS (%)	hazard ratio (HR) (95%CI)	adverse effects
JGOG2041 (Nomura et al.)	II	2011	Patients with measurable disease derived from histologically confirmed stage III/IV or recurrence	DP (70/60), q3w until progression or adverse events	29	72	0/0/31/38[a]	NA	NA	NA (serous+clear+u ndifferentiated : 14)	median PFS: 232 d	median OS: 629 d response rate: 52% (95% CI: 33-71)	neutropenia G3/4: 83%, anorexia G3/4: 17%
				DC (70/AUC6), q3w until progression or adverse events	29	69	0/0/21/59[a]	NA	NA	NA (serous+clear+u ndifferentiated : 14)	median PFS: 238 d	median OS: 731 d response rate: 48% (95% CI: 30-68)	neutropenia G3/4: 90%, anorexia G3/4: 10%
				TC (180/AUC6), q3w, until progression or adverse events	30	90	0/0/17/43/40[a]	NA	NA	NA (serous+clear+u ndifferentiated : 23)	median PFS: 289 d	median OS: 854 d response rate: 60% (95% CI: 41-77)	neutropenia G3/4: 77%, anorexia G3/4: 10%, motor neuropathy: 7%
JGOG2043	III	accrual finished	stage I/II intermediate risk (G2/3 and myometrial invasion >50%), stage III/IV high risk with residual tumors no greater than 2 cm after surgery	AP(60/50) x 6, q3w DP(70/60) x 6, q3w TC (180/AUC6) x 6, q3w	estimated 780								

a: recurrent tumor

Table 2. Randomized trials comparing chemotherapy regimens as an adjuvant therapy for endometrial cancer.

G3/4 adverse effects was lower in the JGOG2033 study. The CAP regimen in the JGOG2033 study, therefore, represented a more modest therapy than that used in the Italian study. Nevertheless, the 5-year PFS rate and OS rate of the high-intermediate risk (HIR) subgroup of the JGOG2033 study were significantly improved by this modest CAP regimen. This means that the cases in the high-intermediate risk (HIR) subgroup of the JGOG2033 study may be good candidates for answering the question, "Which patients with endometrial cancer may benefit from adjuvant chemotherapy?" To answer this question definitively, further evidence is needed from randomized studies investigating the efficacy of adjuvant chemotherapy designed for patients with intermediate- or high-risk endometrial cancer. The modest adjuvant chemotherapy regimen of CAP was superior to pelvic radiotherapy in HIR patients, as defined above; however, this chemotherapy did not have a sufficient efficacy to improve the prognosis of patients with stage III advanced endometrial cancer.

The Italian study[17] revealed no significant differences in the PFS or OS rates among high-risk patients even when a higher-dose CAP regimen was used. The dose of doxorubicin was 60 mg/m² in the GOG122 study[16], 45 mg/m² in the Italian study, and 40 mg/m² in the JGOG2033 study[18].

4.4 What is the best adjuvant chemotherapy for endometrial cancer?

Then, what is the best adjuvant chemotherapy for endometrial cancer? First, let me look back to some studies for advanced or recurrent endometrial cancer.

The response rates to paclitaxel in phase II studies for advanced or recurrent endometrial cancer were reported to be 37.5%[19] and 30.4%[20] in 1996 and 2004, respectively, and the response rates to docetaxel in phase II studies for advanced or recurrent endometrial cancer were reported to be 33%[21] and 31.3%[22] in 2002 and 2005, respectively. These numbers are comparable to the response rates obtained with doxorubicin alone.

In the GOG163 phase III randomized study[23] of AP vs. concomitant doxorubicin + paclitaxel (AT) + G-CSF reported in 2004 on the effects of combining a taxane with doxorubicin or cisplatin, the response rates of 40% vs. 43% revealed no significant differences when compared with the concomitant use of cisplatin, and the median OS was 12.6 months vs.13.6 months, with a HR of 1.00. Furthermore, AT therapy had more disadvantages, such as the need for G-CSF support, compared with AP therapy, and no advantage was found in switching from cisplatin to paclitaxel as the concomitant drug to be used with doxorubicin.

On the other hand, the GOG177 phase III randomized study[24] of AP vs. concomitant paclitaxel + doxorubicin + cisplatin (TAP) + G-CSF reported in the same year (2004) showed that the results of TAP therapy were superior, based on response rates of 34% vs. 57%. The median PFS (8.3 months vs. 5.3 months) and the median OS (15.3 months vs. 12.3 months) were significantly improved in the TAP group. However, in the TAP arm, the incidence of neurotoxicity was significantly higher, and congestive heart failure or treatment-related deaths occurred. Compliance was therefore considered to be poor in view of the toxicity, and TAP therapy has not widely replaced AP as a standard therapy in clinical practice.

Based on the results of the GOG163 study, it seemed that the next steps should be to study the significance of replacing doxorubicin, which has been considered a key drug for a long time, with a taxane and to study which of the two platinum agents should be used. There was thus a need to first study whether or not a regimen combining two agents (taxane + platinum agent) would be better than AP. As there are two taxanes and two platinum agents, whether these regimens or AP therapy would be more effective was investigated in Japan.

Out of the various combinations of the two taxanes and two platinum agents, i.e., TC (paclitaxel + carboplatin), DP (docetaxel + cisplatin), DC (docetaxel + carboplatin), and TP (paclitaxel + cisplatin), the efficacy and safety of the TC, DP, and DC regimens were first compared in JGOG2041, a phase II randomized study[25] (Table 2). TP therapy had already been eliminated, as the results of clinical trials for ovarian cancer revealed a strong neurotoxicity, and a shift from TP to TC therapy had occurred[26-28]. The results revealed the response rates of the three regimens to be in no way inferior to AP therapy, and the toxicity was also within an acceptable range[25].

Based on the results of the JGOG2041 study, a phase III randomized study (JGOG2043) was conducted to compare AP therapy with chemotherapy combining platinum and taxanes in groups with a high risk for the recurrence of endometrial cancer. The results of the JGOG2041 study revealed the response rate of DC therapy (48%) to be somewhat lower, although not significantly, than that of TC therapy (60%) and DP therapy (52%), and TC and DP therapy were therefore selected for comparison with AP therapy in the JGOG2043 study. The groups with a high risk for the recurrence of endometrial cancer in the JGOG2043 study included advanced cases with residual tumors of no greater than 2 cm, and stage I and II cases with invasion to more than half of the myometrium and histological grade 2 or 3 (including serous or clear cell adenocarcinoma), thus allowing the effects on advanced cases and intermediate risk cases to be analyzed separately using sub-analyses. Enrollment in this study was closed at the end of 2010.

In the phase II study, the TC response rate was 60% and the compliance was high (90%). The response rate of TC is therefore being compared with that of TAP (which had the highest response rate in the GOG177 study but had problems in compliance) in patients with advanced or recurrent cancer. The results of the JGOG2041 study, in conjunction with the results of a comparison of the efficacies of TC, DP, and AP in the JGOG2043 study, should prove to be useful for research on the most effective and appropriate chemotherapy regimens. Randomized studies, such as GOG 209 (TAP vs. TC for advanced or recurrent disease) and JGOG 2043 (AP vs. TC vs. DP for adjuvant therapy) are now underway. The TC regimen is widely used both in practical treatment and in research trials for endometrial cancer, based on the promising efficacies reported by various phase II studies, although no evidence of a phase III trial level that certifies TC as a truly standard regimen for endometrial cancer has been obtained.

Chemotherapy has been the mainstream treatment in Japan, but postoperative therapy in Europe is now shifting from the formerly preferred radiation therapy alone to radiation therapy plus chemotherapy. In the US as well, the GOG194 study (closed) for WAI vs. WAI followed by paclitaxel + doxorubicin + cisplatin (TAP therapy) is being conducted to test the effects of combining chemotherapy with radiation therapy as a postoperative treatment regimen for intermediate-risk or high-risk cases.

5. Comparison of radiation therapy alone and the combination of radiation therapy and chemotherapy

Several randomized studies have compared radiation therapy alone and the combination of radiation therapy and chemotherapy as an adjuvant therapy for endometrial cancer (Table 3).

study	phase	year	eligibility	treatment arm	number of cases	compliance rate (%)	percentage of stage I/II/III/IV	percentage of PLN	percentage of PAN	percentage of G3 or serous/clear cell	5-year PFS (%)	5-year OS (%)	hazard ratio (HR) (95%CI)	adverse effects
GOC34 (Morrow et al.)	III	1990	clinically staged I or II (occult) cases who had greater than 50%	EBRT (pelvis ± extended field) 50Gy	89	NA	NA (clinically staged)	100	NA	39 (clear cell 2)	NA	not significant (almost 60% in both arms)	NA	small bowel obstruction: 9%, treatment-related death: 2%
			myometrial invasion, pelvic or aortic node metastasis, cervical involvement, or adnexal metastasis	EBRT (pelvis ± extended field) 50Gy followed by A(45-60)x8 ,q3w (up to max cumulated dose of 500mg)	92	69% (2 or more cycles)	NA (clinically staged)	100	NA	27 (clear cell 5)	NA			small bowel obstruction: 4%, treatment-related death: 3%
Finnish study (Kuoppala et al.)	III	2008	stage IA-B G3, stage IC-IIIA G1-3	EBRT 28Gy (pelvis) x 2 cycle q3w	72	94	69/18/13/0	78	1	33 (serous+clear+undifferentiated: 0)	median DFS: 18 months	disease-specific OS: 85	HR of OS (CT+RT vs RT) : 1.21 (0.56-2.65)	intestinal obstruction: 2% (requiring resection)
				CEP(500/60/50) → EBRT 28Gy (pelvis) → CEP → EBRT28Gy →CEP	84	93	63/25/12/0	82	4	35 (serous+clear+undifferentiated: 0)	median DFS: 25 months	disease-specific OS: 82		nausea G3/4: <8%, leukopenia G3/4: 17%, intestinal obstruction: 10%(requiring resection)
GOG184 (Homesley et al.)	III	2008	initially stage III or IV with disease limited to the pelvis and abdomen (extrapelvic diseases excluded after 2003, except for paraaortic metastasis)	volume-directed radiation followed by AP(45/50) with optional G-CSF x 6 cycles, q3w	288	83	0/0/88/12	NA[a]	NA[a]	40 (serous+clear+undifferentiated :19)	3-y RFS: 62	NA	HR of RFS (RT+TAP vs. RT+AP): 0.90(0.69-1.17) In subgroup analysis of cases with gross residual disease, HR of RFS or death (RT+TAP vs.RT+AP):0.50(0.26-0.92)	neutropenia G3/4: 47%, thrombopenia: 10%, febrile neutropenia: 0%, sensory neuropathy: 2%, myalgia G3/4: 0%
				volume-directed radiation followed by TAP(160/45/50) with G-CSF x 6 cycles, q3w	298	78	0/0/88/12	NA[a]	NA[a]	43 (serous+clear+undifferentiated: 17)	3-y RFS: 64	NA		neutropenia G3/4: 68%, thrombopenia: 25%, febrile neutropenia: 5%, sensory neuropathy: 9%, myalgia G3/4: 3%
(1)+(2) combined NSGO/EORTC and MaNGO/ILAIDE (Hogberg et al.)	III	2010		RT alone	267						69	75 (CSS:78)	HR of PFS (RT+CT vs. RT) :0.63 (0.44-0.89), HR of OS (RT+CT vs.RT) : 0.69 (0.46-1.03), HR of CSS (RT+CT vs.RT): 0.55 (0.35-0.88)	
				RT+CT	267						78[b]	82 (CSS:87[b])		

study	phase	year	eligibility	treatment arm	number of cases	compliance rate (%)	percentage of stage I/II/III/IV	percent age of PLN	percent age of PAN	percentage of G3 or serous/clear cell	5-year PFS (%)	5-year OS (%)	hazard ratio (HR) (95%CI)	adverse effects
(1)NSGO/EORTC55991 (Hogberg et al.)	III	2010	stage I, II, IIIA (positive peritoneal fluid cytology only), or IIIC (positive pelvic lymph nodes only)	EBRT (pelvis 44 Gy) ± vaginal brachytherapy	196	95	90/5/2/0	15	4	48 (serous +clear 40)	72	76 (CSS:79)	HR of PFS (RT+CT vs.RT) :0.64 (0.41-0.99), HR of OS (RT+CT vs. RT) : 0.66 (0.40-1.08), HR of CSS (RT+CT vs.RT): 0.51 (0.28-0.90)	treatment-related death: 0.5%, SAE; intestinal reaction with diarrhea: 0.5% SAE (4%): diarrhea: 1%, neutropenia: 0.5%, neutropenia1.5%, allergic reaction to paclitaxel, 0.5%, atrial fibrillation:0.5%, pulmonary emboli:0.5%
				CT was given before or after CT regimen x4, q3-4w , AP(83%), EP(50 or 75/50) (4%), TEC (175/60/AUC 5) (3%), TC (175/AUC5-6) (10%).	186	73	91/5/2/0	19	3	58 (serous+clear+ana plastic 35)	79[b]	83 (CSS:88[b])		
(2)MaNGO-ILIADEIII	III	2010	stage IIB, IIIA-C disease (stage IIIA with positive cytology alone without other risk factors was not included)	EBRT (pelvis 45 Gy) ± vaginal brachytherapy (if cervical stromal involvement) ± EBRT (paraaortic, if paraaortic metastases)	76	88	0/29/67/0	54	9	45 (anaplastic 1)	61	73 (CSS:76)	HR of PFS (RT+CT vs.RT) :0.61(0.33-1.12), HR of OS (RT+CT vs.RT) : 0.74 (0.36-1.52), HR of CSS (RT+CT vs. RT): 0.65 (0.30-1.44)	no
				AP (60//50)x3, q3w, followed by EBRT (pelvis 45 Gy) ± vaginal brachytherapy ± EBRT (paraaortic)	80	88	0/37/63/0	45	9	34 (serous+clear+ana plastic 4)	74	78 (CSS:82)		leukopenia G3/4: 16%, neutropenia G3/4:30%, nausea and vomiting G3/4: 5%
RTOG-GOG9905	III	accrual finished	endometrioid adenocarcinoma, 1) stage IC and IIA, with ≥50% myometrial invasion, 2) stage IIB, G2-3, <50% serous or clear cell	EBRT / CCRT (P: 2 cycles with pelvic EBRT) followed by TC x 4	estimated 436									
PORTEC III	III	on-going	1) IB G3 with LVSI, IC or IIA G 3, IIB, IIIA or IIIC (IIIA based on cytology alone, only eligible if G3), 2) IB or IC, II or III with serous or clear cell histology	RT arm: EBRT (pelvis 48.6Gy) / RT+CT arm: CCRT(cisplatin 50mg/m², 2 cycles) +TC (175/AUC5) x 4	estimated 500									
GOG249	III	on-going	1) stage I, IIA with high-intermediate risk[c], 2) stage IIB(occult)(any histology) with/without risk factors[c], 3)stage I-IIB(occult) serous or clear cell w/wo other risk features	RT arm: EBRT (pelvis n 45Gy in 25Fr ~ 50.4Gy i 28Fr) (stageI/II clear/serous±optional vaginal cuff boost) / RT+CT arm: brachytherapy followed by TC (175/AUC6) x 3	estimated 562									

a: sampling of PLN or PAN was not required.

b: significantly better

c: 1) G2/3 with LVSI and outer-third myometrial invasion, 2) age of 50 years or greater in addition to any two factors listed above, or 3) age of 70 years or greater with any risk factor listed above.

Table 3. Randomized trials comparing radiation therapy with combination of radiation therapy and chemotherapy as an adjuvant therapy for endometrial cancer.

5.1 GOG34

This study was the first randomized trial to compare radiation alone and radiation followed by chemotherapy[29]. The subjects were comprised of patients with clinical stage I or II (occult) disease in whom surgical-pathologic evaluation had revealed one or more risk factors for recurrence: a greater than 50% myometrial invasion, pelvic or aortic node metastasis, cervical involvement, or adnexal metastases. The patients received 50-Gy EBRT with or without paraaortic radiation and were then randomized into two arms: no further therapy or additional doxorubicin (45 – 60 mg/m^2) every three weeks to a maximum cumulative dose of 500 mg/m^2. No statistically significant difference in the OS or PFS was observed between the two arms. Unfortunately, because of protocol violations, the small sample size, and the number of patients lost to follow-up, this study was unable to determine what effect the use of doxorubicin as an adjuvant therapy had on recurrence, progression, and survival.

5.2 Finnish study

For the Finnish study[30], surgically staged IA-B G3 cases or stage IC-IIIA G1-3 cases were enrolled and randomized to receive pelvic EBRT alone (28 Gy x 2 cycles) or a unique combination of alternating EBRT and chemotherapy, namely, a first cycle of CEP (cyclophosphamide 500 mg/m^2; epirubicin, 60 mg/m^2; and cisplatin, 50 mg/m^2) followed by a first cycle of EBRT (28 Gy), a second cycle of CEP, a second cycle of EBRT (28 Gy), and finally a third cycle of CEP. However, this study failed to reveal an improvement in the OS or PFS by the addition of chemotherapy to radiation therapy. Moreover, adverse events such as severe bowel obstruction requiring surgery tended to occur more frequently in the combined treatment arm.

5.3 GOG 184

For the GOG184 study[31], surgically staged III or IV cases were enrolled and treated with volume-directed irradiation of the pelvic/para-aortic lymph nodes. The patients were subsequently randomized to compare the recurrence-free survival (RFS) and toxicity between two chemotherapy regimens. Treatment was randomized between six cycles of cisplatin (50 mg/m^2) and doxorubicin (45 mg/m^2) with or without paclitaxel (160 mg/m^2). The accrual of stage IV patients was completed in June, 2003. Approximately 80% of the subjects completed six cycles of chemotherapy. Three deaths resulted from bowel complications, and one death was caused by renal failure. Hematologic adverse events, sensory neuropathy, and myalgia, were more frequent and severe in the paclitaxel arm ($P < 0.01$). The percentage of patients alive and recurrence-free at 36 months was 62% for RT + AP vs. 64% for RT + TAP. The hazard of recurrence or death relative to the RT + AP arm and stratified according to stage was 0.90 (95% CI, 0.69 to 1.17; $P = 0.21$). However, in a subgroup analysis, RT + TAP was associated with a 50% reduction in the risk of recurrence or death among patients with gross residual disease (95% CI, 0.26 to 0.92). This study showed that the addition of paclitaxel to cisplatin and doxorubicin following surgery and radiation was not associated with a significant improvement in RFS but was associated with increased toxicity.

5.4 NSGO 9501/ EORTC 55991 study and MaNGO ILIADE III study

Hogberg et al. reported a paper[32], presenting two randomized clinical trials (NSGO EC9501 /EORTC55991 and MaNGO ILIADEIII). The former study was reported at the ASCO 2007

meeting[33]). These two studies were undertaken to clarify whether the sequential combination of chemotherapy and radiotherapy improves the PFS in high-risk subjects with endometrial cancer. These studies had similar designs; however, some differences existed regarding the distribution of stages and the rates of pelvic or paraaortic lymphadenectomy. Most of the enrolled cases were stage I in the former study, while all the cases were stage II or III in the latter study; in addition, the rate of pelvic or paraaortic lymphadenectomy was higher in the ILIADEIII study. In total, patients (n = 540) with surgically resected endometrial cancer stage I – III and with no residual tumor or prognostic factors implying a high -risk were randomly allocated to an adjuvant radiotherapy group with or without sequential chemotherapy.

In the NSGO/EORTC study, patients with stage I, II, IIIA (positive peritoneal fluid cytology only), or IIIC (positive pelvic lymph nodes only) diseases were enrolled. The chemotherapy modalities included AP (doxorubicin, 50 mg/m^2 + cisplatin, 50 mg/m^2; 83%), EP (epirubicin, 75 mg/m^2; 4%), TEC (paclitaxel, 175 mg/m^2 + epirubicin, 60 mg/m^2 + carboplatin, AUC 5; 3%), and TC (paclitaxel, 175 mg/m^2, carboplatin, AUC 5 – 6; 10%). The radiation arm consisted of pelvic EBRT (44 Gy) with or without brachytherapy. The combined modality treatment was associated with a 36% reduction in the risk of relapse or death (HR, 0.64; 95% CI, 0.41 – 0.99; P = 0.04); two-sided tests were used. In the MaNGO ILIADEIII study, only the AP therapy was used as a chemotherapy regimen. The results from the MaNGO ILIADEIII study pointed in the same direction (HR, 0.61) as those of the NSGO/EORTC study, but were not significant. In both studies, adverse effects were more severe in the combined modality group.

In the combined analysis, the estimate of the risk for relapse or death was similar but with narrower confidence limits (HR, 0.63; 95% CI, 0.44 – 0.89; P = 0.009). Neither study showed significant differences in the OS. In the combined analysis, the OS approached statistical significance (HR, 0.69; 95% CI, 0.46 – 1.03; P = 0.07) and cancer-specific survival (CSS) was significant (HR, 0.55; 95% CI, 0.35 – 0.88; P = 0.01). Thus, the addition of adjuvant chemotherapy to radiation improved the PFS and CSS in surgically treated endometrial cancer patients with no residual tumor and a high-risk profile. Regarding the pathological subtypes, combined therapy offered a superior benefit to patients with endometrioid type and grade 1 or 2 diseases, but not to patients with serous or clear cell types and grade 3 diseases. Several remaining questions need to be further investigated in future trials.

6. Ongoing trials comparing radiation therapy alone and radiation therapy plus chemotherapy

At present, there are several ongoing studies comparing radiation therapy alone and radiation plus chemotherapy (Table 3). The RTOG-GOG9905 study finished accrual in 2004; however, its results have not yet been presented. Accrual for the PORTECIII and GOG249 trials is ongoing. These three trials are phase III randomized trials comparing a radiation alone group and a combined radiation and chemotherapy group. Two of them are examining concurrent chemoradiotherapy followed by four cycles of TC, and the third trial is examining brachytherapy followed by three cycles of TC.

7. Conclusions

As described above, many problems regarding adjuvant therapy for endometrial cancer remain. (1) Which patients receive the highest benefit from adjuvant therapy? (2) Is there a

definite consensus regarding the criteria for grouping patients according to the risk of recurrence? (3) Which chemotherapy regimen should be certified as the gold standard regimen for adjuvant therapy based on the results of phase III randomized trials? (4) Which combination of radiation therapy and chemotherapy is best? To answer these questions, before designing a trial concept, a worldwide consensus on the criteria for risk groups needs to first be obtained. In addition, to interpret the results of various adjuvant therapy trials, careful attention to the kind of surgery that the patients have received and the percentages of grade 3 endometrioid adenocarcinoma and aggressive pathological subtypes (serous, clear cell, undifferentiated, and so on) is needed. In this review, as shown in Tables 1, 2, and 3, we have collected information regarding the percentages of pelvic lymphadenectomy, paraaortic lymphadenectomy, grade 3 endometrioid adenocarcinoma or aggressive pathological subtypes, and informations about surgical stage distribution, treatment compliance, and adverse effects. Before arguing the results of clinical trials, sufficient information regarding the patient conditions after surgery and just before receiving adjuvant therapy is needed. For example, some trials with low percentages of pelvic or paraaortic lymphadenectomy, trials with high percentages of G3 or aggressive pathological subtypes, and trials with high percentages of advanced stage patients tend to favor chemotherapy, since these patient groups tend to have higher possibilities of micrometastases that cannot be identified using imaging.

The results of ongoing studies, such as GOG0237 (TAP vs. TC, advanced or recurrent disease, phase III) and JGOG2043 (AP vs. DP vs. TC, adjuvant, phase III) may provide important information regarding question (3) above, and the results of the RTOG-GOG9905, PORTECIII, and GOG249 studies may help to answer question (4). Further studies are needed to resolve question (1).

8. References

[1] Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, Ngan HY, Sideri M, Pecorelli S. Carcinoma of the corpus uteri. J Epidemiol Biostat. 2001;61:47-86.

[2] Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, Graham JE. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1991 ;40:55-65.

[3] Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, Miller A, Blessing JA. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstet Gynecol. 1984;63:825-32.

[4] Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC. Endometrial cancer: predictors of peritoneal failure. Gynecol Oncol. 2003;89:236-42.

[5] National Comprehensive cancer Network: Clinical practice guideline in oncology. Uterine cancers. Version1. 2012;
http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

[6] Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980;56:419-27.

[7] Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van de Steen-Banasik E,

Beerman H, van Lent M. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355:1404-11.

[8] Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, Pearlman A, Maiman MA, Bell JG; Gynecologic Oncology Group. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004 ;92:744-51.

[9] ASTEC/EN.5 Study Group, Blake P, Swart AM, Orton J, Kitchener H, Whelan T, Lukka H, Eisenhauer E, Bacon M, Tu D, Parmar MK, Amos C, Murray C, Qian W. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet. 2009;373:137-46.

[10] Thigpen JT, Buchsbaum HJ, Mangan C, Blessing JA. Phase II trial of adriamycin in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Cancer Treat Rep. 1979 ;63:21-7.

[11] Tropé C, Johnsson JE, Simonsen E, Christiansen H, Cavallin-Ståhl E, Horváth G. Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. Am J Obstet Gynecol. 1984 ;149:379-81.

[12] Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, Liao S. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol. 2004 ;22:3902-8.

[13] Aapro MS, van Wijk FH, Bolis G, Chevallier B, van der Burg ME, Poveda A, de Oliveira CF, Tumolo S, Scotto di Palumbo V, Piccart M, Franchi M, Zanaboni F, Lacave AJ, Fontanelli R, Favalli G, Zola P, Guastalla JP, Rosso R, Marth C, Nooij M, Presti M, Scarabelli C, Splinter TA, Ploch E, Beex LV, ten Bokkel Huinink W, Forni M, Melpignano M, Blake P, Kerbrat P, Mendiola C, Cervantes A, Goupil A, Harper PG, Madronal C, Namer M, Scarfone G, Stoot JE, Teodorovic I, Coens C, Vergote I, Vermorken JB; European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Ann Oncol. 2003;14:441-8.

[14] Dunton CJ, Pfeifer SM, Braitman LE, Morgan MA, Carlson JA, Mikuta JJ. Treatment of advanced and recurrent endometrial cancer with cisplatin, doxorubicin, and cyclophosphamide. Gynecol Oncol. 1991;41:113-6.

[15] Thigpen JT, Blessing JA, DiSaia PJ, Yordan E, Carson LF, Evers C. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. J Clin Oncol. 1994 ;12:1408-14.

[16] Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, Thigpen JT, Benda JA; Gynecologic Oncology Group Study. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2006 ;24:36-44.

[17] Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, Colombo A, Fossati R. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer. 2006 ;95:266-71.

[18] Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, Kudo R; Japanese Gynecologic Oncology Group. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol. 2008;108:226-33.

[19] Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1996 ;62:278-81.

[20] Hirai Y, Hasumi K, Onose R, Kuramoto H, Kuzuya K, Hatae M, Ochiai K, Nozawa S, Noda K. Phase II trial of 3-h infusion of paclitaxel in patients with adenocarcinoma of endometrium: Japanese Multicenter Study Group. Gynecol Oncol. 2004 ;94:471-6.

[21] Gordon AN, Hart DJ, Bailey C, Anthony S, Surwit EA. Phase II trial of docetaxel in recurrent or advanced endometrial carcinoma. Ann Oncol. 2002 ;13: (suppl 5):109.

[22] Katsumata N, Noda K, Nozawa S, Kitagawa R, Nishimura R, Yamaguchi S, Aoki D, Susumu N, Kuramoto H, Jobo T, Ueki K, Ueki M, Kohno I, Fujiwara K, Sohda Y, Eguchi F. Phase II trial of docetaxel in advanced or metastatic endometrial cancer: a Japanese Cooperative Study. Br J Cancer. 2005 ;93:999-1004.

[23] Fleming GF, Filiaci VL, Bentley RC, Herzog T, Sorosky J, Vaccarello L, Gallion H. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. Ann Oncol. 2004;15:1173-8.

[24] Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, Kline R, Burger RA, Goodman A, Burks RT. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2004;22:2159-66.

[25] Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, Mannel RS, DeGeest K, Hartenbach EM, Baergen R; Gynecologic Oncology Group. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2003 ;21:3194-200.

[26] du Bois A, Lück HJ, Meier W, Adams HP, Möbus V, Costa S, Bauknecht T, Richter B, Warm M, Schröder W, Olbricht S, Nitz U, Jackisch C, Emons G, Wagner U, Kuhn W, Pfisterer J; Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst. 2003;95:1320-9

[27] Neijt JP, Engelholm SA, Tuxen MK, Sorensen PG, Hansen M, Sessa C, de Swart CA, Hirsch FR, Lund B, van Houwelingen HC. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. J Clin Oncol. 2000;18:3084-92.

[28] Nomura H, Aoki D, Takahashi F, Katsumata N, Watanabe Y, Konishi I, Jobo T, Hatae M, Hiura M, Yaegashi N. Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients

with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Ann Oncol. 2011 ;22:636-42.

[29] Morrow CP, Bundy BN, Homesley HD, Creasman WT, Hornback NB, Kurman R, Thigpen JT. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group Study Gynecol Oncol. 1990;36:166-71.

[30] Kuoppala T, Maenpaa J, Tomas E, Puistola U, Salmi T, Grenman S, Lehtovirta P, Fors M, Luukkaala T, Sipila P. Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. Gynecol Oncol. 2008;110:190-5.

[31] Homesley HD, Filiaci V, Gibbons SK, Long HJ, Cella D, Spirtos NM, Morris RT, DeGeest K, Lee R, Montag A. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol. 2009 ;112:543-52.

[32] Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, Andersson H, Grenman S, Lundgren C, Rosenberg P, Boman K, Tholander B, Scambia G, Reed N, Cormio G, Tognon G, Clarke J, Sawicki T, Zola P, Kristensen G. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer. 2010;46:2422-31.

[33] Hogberg T, Rosenberg P, Kristensen G, de Oliveira CF, de Pont Christensen R, Sorbe B, Lundgren C, Salmi T, Andersson H, and Reed NS. A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991) J Clin Oncol. 2007; 25 (18 suppl): #5003 (ASCO Annual Meeting Proceedings)
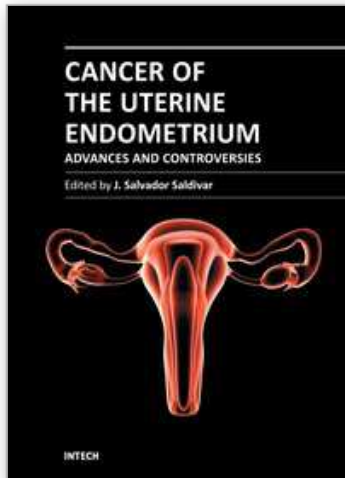
Cancer of the Uterine Endometrium - Advances and Controversies

Edited by Dr J.S. Saldivar

ISBN 978-953-51-0142-0

Hard cover, 182 pages

Publisher InTech

Published online 29, February, 2012

Published in print edition February, 2012

The book Cancer of the Uterine Endometrium - Advances and Controversies brings together an international collaboration of authors who share their contributions for the management of endometrial carcinoma. The scope of the text is not basic, but rather aims to provide a comprehensive and updated source of advances in the diagnosis and therapeutic strategies in this field of gynecologic cancer. Each section in the book attempts to provide the most relevant evidence-based information in the biology and genetics, modern imaging, surgery and staging, and therapies for endometrial cancer. It is hoped that future editions will bring additional authors to contribute to this endeavor. To this end, it is our patients who will benefit from this work.

INTECH

open science | open minds