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Treatment Strategies and Prognosis of Endometrial Cancer

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1. Introduction

Endometrial cancer is the fourth most common cancer and the most common gynecological cancer diagnosed in the women in the United States. The lifetime risk of developing endometrial cancer is 2.58% in US women. The American Cancer Society estimates approximately 47,000 new cases and 8,120 deaths due to endometrial cancer in 2011 (Siegel et al. 2011). There does appear to be a significant difference in prognosis based on race. The incidence of endometrial cancer is higher in white women compared to the black women (age adjusted incidence rate: 24.8 vs. 20.9 per 100,000 women), but the death rate from endometrial cancer in the black women is almost two times that of the white women (age adjusted death rate: 3.9 vs. 7.2 per 100,000 women) (Howlader N). Furthermore, the incidence and the death rate have remained stable in the white women; although it has been rising steadily in the black women (by 1.7% per year and 0.8% per year, respectively) (Howlader N).

The management strategies in endometrial cancer have evolved dramatically in the past two decades. Despite the advances in the treatment of endometrial cancer; the death rate from endometrial cancer remains high. Clearly, more effective treatment strategies are needed.

2. Histological classification

Endometrial cancer can be divided into two histologic subtypes: Type I and Type II. Type I endometrial cancers account for the majority of uterine cancer cases and occur more commonly in association with overexposure to estrogen. They are of endometrioid histology, diagnosed in early stages, and are commonly associated with K-ras, PTEN, and/or mismatch repair gene mutations. They are also associated with obesity. Type II endometrial cancers, on the other hand, are typically of aggressive non endometrioid histology and are therefore more commonly diagnosed in advanced stages. They often develop in a background of atrophic endometrium (Bokhman 1983) and have a greater probability of having p53 mutations and/or HER2/neu over expression (Prat et al. 2007).

3. Management of endometrial cancer

The primary treatment of endometrial cancer is surgical. Following tissue diagnosis, most patients are offered surgical staging. Routine preoperative work-up includes complete blood count, serum electrolytes/ creatinine, liver function tests, urinalysis, and a CXR. Further evaluation with CT/MRI/PET-CT (with or without CA-125) may be performed, if extrauterine disease is suspected on initial assessment. In patients with suspected cervical involvement, MRI or cervical biopsy may be helpful to confirm the diagnosis (Akin et al. 2007).

3.1 Surgical staging and related issues

In 1988 the FIGO staging committee replaced the clinical staging system for endometrial cancer with a surgical staging system. This transition from clinical to surgical staging was mainly due to the seminal findings of a large gynecologic oncology group trial (GOG 33), which evaluated the surgical-pathologic patterns in apparent early stage endometrial cancer with particular emphasis on pelvic and para-aortic lymph node involvement (Creasman et al. 1987). A significant number (25%) of patients with clinical stage I in this study were found to have extrauterine disease upon comprehensive surgical staging.

The 1988 FIGO staging system was recently modified (Pecorelli et al. 2009). These two staging criteria are shown in Tables 1 and 2 respectively.

Stage IA G123	Tumor limited to the endometrium
Stage IB G123	Invasion to less than half of the myometrium
Stage IC G123	Invasion equal to or more than half of the myometrium
Stage IIA G123	Endocervical glandular involvement only
Stage IIB G123	Cervical stromal invasion
Stage IIIA G123	Tumor invades serosa and/or adnexa and/or positive peritoneal cytology
Stage IIIB G123	Vaginal metastasis
Stage IIIC G123	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IVA G123	Tumor invasion of bladder and/or bowel mucosa
Stage IVB G123	Distant metastasis including intra-abdominal metastasis and/or inguinal lymph nodes

Table 1. 1988 FIGO Surgical Staging for Endometrial Cancer.

Stage IA G123	Invasion to less than half of the myometrium
Stage IB G123	Invasion equal to or more than half of the myometrium
Stage II G123	Cervical stromal invasion
Stage IIIA G123	Tumor invades serosa and/or adnexa
Stage IIIB G123	Vaginal metastasis
Stage IIIC1 G123	Metastasis to pelvic lymph nodes
Stage IIIC2 G123	Metastasis to para-aortic lymph nodes
Stage IVA G123	Tumor invasion of bladder and/or bowel mucosa
Stage IVB G123	Distant metastasis including intra-abdominal metastasis and/or inguinal lymph nodes

Table 2. 2009 FIGO Surgical Staging for Endometrial Cancer.

The current standard surgical staging procedure includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, peritoneal washings for cytology, and meticulous exploration of the abdomen and pelvis with biopsy of any suspicious lesions (NCCN guidelines for uterine neoplams, V.2.2011) (NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Uterine Neoplasms V.2.2011. © 2011 National Comprehensive Cancer Network). This procedure has been shown feasible by laparoscopy. In LAP-2 trial; the pelvic and para-aortic lymph nodes were obtained in 96% patients undergoing laparotomy compared to 92% of those who had laparoscopy (p<0.001). The detection rate of advanced stage was also comparable between the groups (17% vs. 17%, p=0.841) (Walker et al. 2009).

GOG 33 identified that depth of myometrial invasion, and tumor grade were predictive of lymph node metastasis (Creasman et al. 1987) and that all were predictive of recurrence. The preoperative and intra-operative evaluation of these high-risk features is often inaccurate, and surgical staging is therefore recommended in most patients diagnosed with endometrial cancer (NCCN guidelines for uterine neoplasms, V.2.2011).

The preoperative tumor grade was upgraded on final pathology in approximately 18% patients in different studies (Goudge et al. 2004) (Ben-Shachar et al. 2005). Neither imaging nor frozen section is very accurate for assessing the depth of myometrial invasion. In a recent study by Case et al, concordance between frozen and final pathology was noted only in 67% patients for depth of myometrial invasion and 58% patients for tumor grade (Case et al. 2006). The sensitivity of MRI has similarly been found to be only 54%-75% in this regard (Hricak et al. 1991; Nakao et al. 2006).

The use of imaging (CT, MRI, and PET-CT) has been evaluated for the pre-operative assessment of lymph node metastasis in endometrial cancer. Park et al showed that the sensitivity and specificity of MRI and PET-CT was only modest (46% and 88%; and 69% and 90%, respectively) (Park et al. 2008). Palpation of lymph nodes is also not reliable, with a false negative rate of over 35% in some studies (Girardi et al. 1993; Arango et al. 2000). Intra-operative frozen section evaluation was found to miss nearly 2/3rds of endometrial cancer patients with positive lymph nodes, in a recent study (Pristauz et al. 2009).

Several retrospective studies have shown an improvement in survival following pelvic and para-aortic lymphadenectomy (Kilgore et al. 1995; Mohan et al. 1998; Trimble et al. 1998; Cragun et al. 2005; Chan et al. 2006). In contrast, no survival benefit could be demonstrated in either of the two recent prospective randomized controlled trials (Kitchener et al. 2009; Panici et al. 2008). The ASTEC trial recruited 1,408 women with early stage endometrial cancer from 85 centers across four countries (U.K., Poland, New Zealand, and South Africa) (Kitchener et al. 2009). These women were randomized to undergo surgery either with or without lymphadenectomy. To control for postsurgical treatment, women with intermediate or high risk of recurrence were randomized into the ASTEC radiotherapy trial. No survival benefit was observed from pelvic lymphadenectomy in this trial. The 5-year overall survival was 81% in the surgery only group and 80% in the surgery plus lymphadenectomy group (HR: 1.04, CI: 0.74-1.45, p=0.83). The corresponding 5-year recurrence free survival was 79% and 73%, respectively (HR: 1.25, CI: 0.93-1.66, p=0.14). In another randomized study from Italy, 514 patients with preoperative FIGO stage I endometrial carcinoma were evaluated (Panici et al. 2008). At a median follow-up of 49 months, the rates of disease free survival

(81.0% vs. 81.7%, HR: 1.20, CI: 0.75-1.91) and overall survival (85.9% vs. 90.0%; HR: 1.16, CI: 0.67-2.02) were not significantly different between the lymphadenectomy and the no-lymphadenectomy arms. Although, these trials have been criticized for various shortcomings (Amant et al. 2009; Uccella et al. 2009; Uccella et al. 2009); they constitute level one evidence and indicate that lymphadenectomy by itself does not provide survival advantage in endometrial cancer.

The morbidity associated with surgical staging has been reported in several studies (Moore et al. 1989; Larson and Johnson 1993; Franchi et al. 2001). In a study of 168 patients with endometrial cancer; the short term complications after complete surgical staging included fever (31.5%), surgical site infection (4.7%), embolic events (1.3%), and death (0.7%). The late complications in this series were leg edema (0.7%), intestinal obstruction (0.7%), and lymphocysts (1.3%) (Larson et al. 1993). In another study by Cragun et al, adverse events were noted in 18% patients. The most common complications were illeus (2.6%), deep venous thrombosis (2.6%), lymphocysts (2.4%), and small bowel obstruction (1.8%) (Cragun et al. 2005). The postoperative morbidity after surgical staging was significantly less in patients undergoing laparoscopy compared to those who had the procedure performed via laparotomy (14% vs. 21%, p<0.001) in the LAP-2 trial (Walker et al. 2009). To further limit the morbidity associated with complete lymph node dissection; sentinel lymph node detection is being evaluated in endometrial cancer (Gien et al. 2005; Delaloye et al. 2007; Frumovitz et al. 2007). Though controversial worldwide, FIGO staging remains the standard at this time as it allows for more accurate post surgical treatment.

3.2 Treatment after surgical staging

Treatment after initial staging depends on the final stage assigned after regarding different surgical-pathologic risk factors. It is discussed here under three broad headings: treatment of stage I endometrial cancer; treatment of endometrial cancer with cervical involvement (stage II); and treatment of advanced stage endometrial cancer(stages III and IV) (Table 3).

3.2.1 Treatment of stage I endometrial cancer

3.2.1.1 Low-risk patients

Patients with no myometrial invasion and grade 1/2 disease have particularly low risk of recurrence (2-10%) (Creasman et al. 1987). Neither pelvic external beam radiotherapy nor vaginal brachytherapy is recommended for these patients. In a recent study, no vaginal recurrences were reported in these patients after surgery alone (Straughn et al. 2002).

3.2.1.2 Intermediate risk

Intermediate risk endometrial cancer is divided into low-intermediate risk and high-intermediate risk disease. Low-intermediate risk group includes patients with no myometrial invasion and grade 3 disease; patients with less than 50% myometrial invasion and grade 1/2 disease. High-intermediate risk group includes patients with less than 50% myometrial invasion and grade 3 disease; patients with myometrial invasion ≥50% and grade 1/2 disease; and patients with stage IIA disease and grade 1/2 disease.

Stage	Adverse risk factors	Adjuvant Treatment		
		G1	G2	G3
Stage IA	Absent	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
	Present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT
Stage IB	Absent	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or Pelvic RT
	Present	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Pelvic RT and/or Vaginal brachytherapy ± Chemotherapy
Stage II	---	Vaginal brachytherapy and/or Pelvic RT	Pelvic RT + Vaginal brachytherapy	Pelvic RT + Vaginal brachytherapy ± Chemotherapy
Stage IIIA	---	Chemotherapy ± RT or Tumor-directed RT± Chemotherapy or Pelvic RT ± Vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT± Chemotherapy or Pelvic RT ± Vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT± Chemotherapy or Pelvic RT ± Vaginal brachytherapy
Stage IIIB	---	Chemotherapy and/or Tumor-directed RT	Chemotherapy and/or Tumor-directed RT	Chemotherapy and/or Tumor-directed RT
Stage IIIC1, IIIC2	---	Chemotherapy and/or Tumor-directed RT	Chemotherapy and/or Tumor-directed RT	Chemotherapy and/or Tumor-directed RT
Stage IVA, IVB	---	Chemotherapy ± RT	Chemotherapy ± RT	Chemotherapy ± RT

1: All staging is based on updated 2009 FIGO staging.
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Table 3. NCCN Guidelines for Adjuvant Treatment in Endometrial Cancer.

Patients in intermediate risk group have been the subjects of different randomized controlled trials (Table 4). The Norwegian trial led by Aalders et al recruited 540 stage I patients between 1968-1974 (Aalders et al. 1980). All patients underwent surgery and subsequently received vaginal brachytherapy at the dose of 60 Gy. Patients were then randomized to receive either external beam radiotherapy (EBRT) or no further treatment (NFT). The vaginal and pelvic recurrence rate was higher in the observation arm compared to the radiotherapy arm (7% vs. 2%, p=0.01). Interestingly, the distant failure rate was higher in the radiotherapy group than the control group (10% vs. 5%, p=0.05). The 5-year overall survival was not different between the groups. A distinct survival advantage was observed

on subgroup analysis among patients with grade 3 tumor and deep myometrial invasion who had received RT (Aalders et al. 1980).

PORTEC-1 included stage I endometrial cancer patients with either: grade I disease and deep myometrial invasion (≥50%); grade II disease with any myoinvasion; or grade III disease with superficial (<50%) myometrial invasion (Creutzberg et al. 2000). A total of 715 patients were enrolled. All patients underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy without lymph node dissection. Subsequently, these patients were randomized to external beam radiotherapy or no further treatment. The loco-regional recurrence rate was significantly lower in the EBRT arm compared to the NFT arm (4% vs. 14%, p<0.001). The distant recurrence rate, the 5-year overall survival rate, and the endometrial cancer related death rate were however comparable (p≥0.05). Treatment related complications were more common in the radiotherapy group compared to the control group (25% vs. 6%, p<0.001). Scholten et al published a 10-year follow-up of PORTEC-1, which excluded cases downgraded after central pathology review (Scholten et al. 2005). Similar to the original study, the 10-year loco-regional relapse rate was significantly higher in the no further treatment group compared to the RT group (14% vs. 5%, p>0.001). Radiation was particularly effective in patients with two out of the following three high-risk features (age >60 years, > 50% myometrial invasion, and grade III)--loco-regional recurrence rate 4% in the RT group vs. 23% in the control group. Most loco-regional recurrences however were isolated vaginal recurrences, with higher salvage rate in control group versus the RT group (70% vs. 38%).

The Gynecologic Oncology Group also evaluated the role of adjuvant pelvic radiotherapy in patients with early stage endometrial cancer (GOG 99) (Keys et al. 2004). This trial included patients with stage IB, IC, and stage II (occult) disease. Patients with clear cell and papillary serous endometrial cancers were excluded. All patients were required to undergo a complete surgical staging procedure. Afterwards, patients were randomized to either no further treatment or external beam radiation. Based on the following risk factors: age, lymphovascular space invasion, grade III tumors, and outer third myometrial invasion; a high intermediate risk group was defined including patients aged ≥70 years with ≥1 risk factor; 50-70 years with ≥ 2 risk factors; or <50 years with all three risk factors. All other patients were considered low-intermediate risk. The median follow up was 69 months. The two year cumulative incidence of recurrence was 12% in the no additional treatment arm and 3% in the RT arm (relative hazard=0.42, p=0.007). Majority of the difference between the two groups could be explained on the basis of disparity in the occurrence of vaginal recurrences (13 in the NFT arm and 2 in the RT arm). The overall survival was not significantly different between the RT and the NFT groups (p=0.56). On subgroup analysis, RT resulted in statistically significant improvement in the incidence of recurrence in the high intermediate risk group (2 year CIR: 6% VS. 26%; relative hazard 0.42, 90% CI: 0.21-0.83), but not in the low-intermediate risk group (2 year CIR: 2% VS. 6%; relative hazard: 0.46, 90% CI: 0.19-1.11). However, patients in the RT group experienced more frequent and more severe toxicities, and the difference was particularly significant for hematologic, gastrointestinal, genitourinary, and cutaneous toxicities.

ASTEC/EN.5 trial enrolled 905 women between 1996-2005 with node negative early stage endometrial cancer (stages I-IIA) and intermediate or high risk features (IA grade 3, IB all grades, papillary serous or clear cell histology all stages and grades) (Blake et al. 2009). After

surgery, brachytherapy was allowed to all patients according to the local policy. Patients were then randomized to either EBRT or observation. There was no difference between groups in regards to either overall survival (5-year OS: 84% in both groups; HR 1.05 CI: 0.75-1.48, p=0.77) or recurrence free survival (84.7% NFT vs. 85.3% EBRT; HR: 0.92 CI: 0.66-1.31). The 5-year cumulative incidence of isolated vaginal or pelvic recurrence was 6.1% in the NFT arm and 3.2% in the EBRT arm (HR 0.46 CI: 0.24-0.89, p=0.02). Both acute (57% vs. 27%) and late toxicity (61% vs. 45%) was significantly more in the EBRT group compared to the observation group.

Based on the results of these trials, it appears that radiotherapy decreases the incidence of loco-regional recurrence but does not improve survival. The reduction of loco-regional recurrences is mainly due to a decrease in the incidence of vaginal recurrences which accounted for almost 75% of all locoregional recurrences in the control arm. Given the adverse effects noted with radiation, a randomized PORTEC-2 trial was opened to investigate if vaginal brachytherapy would be as effective as EBRT (Nout et al. 2010). Patients at high-intermediate risk for recurrence were eligible for enrollment (age >60 years and IC grade 1/2 disease or stage IB grade 3 disease; stage IIA any age (apart from grade 3 with >50% myometrial invasion). All patients underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy without lymphadenecetomy. Subsequently, patients were randomized to receive either pelvic RT or vaginal brachytherapy. The 5-year vaginal recurrence rate was 1.8% in the vaginal brachytherapy group (VBT) and 1.6% in the EBRT group (HR=0.78 CI: 0.17-3.49; p=0.74). Although, pelvic recurrence rate was higher in the VBT arm (3.8% vs. 0.5%; p=0.02); there was no difference between groups regarding the incidence of either locoregional recurrence (EBRT: 2.1% vs. VBT: 5.1%; p=0.17), distant recurrence (EBRT: 5.7% vs. VBT: 8.3%; p=0.46), or survival (5-year overall survival: 79.6% in EBRT vs. 84.8% in VBT; p=0.57). The gastrointestinal side effects were however significantly more common in the EBRT group compared to the VBT group (53.8% v12.6%, respectively) with resultant poorer quality of life (Nout et al. 2009).

First Author, yr (Reference study)	N	Stages	LND	Treatment	LRR	DRR	5-yr OS
1. Aalders et al, 1980 (Norwegian)	540	I	No	Sx + VBT	7%[1]	5%	91%
				Sx + VBT + EBRT	2%[1]	10%	89%
2. Creutzberg et al, 2000 (PORTEC-1)	715	I	No	Sx	14%[1]	7%	85%
				Sx + EBRT	4%[1]	8%	81%
3. Keys et al, 2004 (GOG 99)	342	I-II	Yes	Sx	7%[1]	8%	86%[2]
				Sx + EBRT	2%[1]	5%	92%[2]
4. Blake et al, 2009 (ASTEC/EN.5)	905	I-II	No	Sx	6%	--	84%
				Sx + EBRT	3%	--	84%
5. Nout et al, 2010 (PORTEC-2)	427	I-II	No	Sx + VBT	5%	8%	85%
				Sx + EBRT	2%	6%	80%

1: Statistically significant difference; 2: 4-yr OS
LND: Lymph Node Dissection; LRR: Locoregional Recurrence Rate; DRR: Distant Recurrence Rate
Sx: Surgery; VBT: Vaginal Brachytherapy; EBRT: External Beam Radiotherapy
GOG: Gynecologic Oncology Group

Table 4. Randomized Controlled Trials of Adjuvant Radiotherapy in Early Stage Endometrial Cancer.

These data suggest that vaginal brachytherapy could be used as effectively as external beam RT to optimize local control in patients deemed to be at high-intermediate risk, and with less morbidity and better quality of life.

3.2.1.3 High risk patients

High risk endometrial cancer includes patients with 1988 FIGO stage IC with grade 3 disease and/or lymphovascular space invasion; 1988 FIGO stage IIA with grade 3 disease, deep myometrial invasion, and/or lymphovascular space invasion; stages IIB, III and IV; clear cell or papillary serous histologies. Creutzberg et al compared 104 patients with stage IC grade 3 endometrial cancer against the PORTEC patients who received RT (Creutzberg et al. 2004). The locoregional recurrence rate was 1-3% among the PORTEC patients, and 14% for stage IC grade 3 patients. The 5-year distant metastasis rates were 3-8% for grade 1/2 patients, 20% for stage IB grade III patients, and 31% for stage IC grade III patients. The high-risk patients remain at significant risk for distant failure despite EBRT. In an attempt to improve distant failure rate and survival in these patients, the use of adjuvant chemotherapy has been explored in several clinical trials (Table 5). The results of most of these trials have been negative with the exception of two trials (Randall et al. 2006 and Hogberg et al. 2010).

First Author, yr (Reference Study)	N	Stages	Treatment	5-yr PFS	5-yr OS
1. Morrow et al, 1990	181	I-II	Sx + XRT	--	60%
(GOG 34)			Sx + XRT + A	--	60%
2. Maggi et al, 2006	345	I-III	Sx + CAP	63%	66%
			Sx + XRT	63%	69%
3. Susumu et al, 2008	385	I-III	Sx + CAP	82%	87%
(JGOG)			Sx + XRT	84%	85%
4. Kuoppala et al, 2008	156	I-III	Sx + XRT	---	85%
(Finnish)			Sx + XRT + CAP	---	82%
5. Hogberg et al, 2010	534	I-III	Sx + XRT	69%[1]	75%
(Combined NSGO/EORTC and MaNGO/ILIADE III)			Sx + XRT + CT	78%[1]	82%

1: Statistically significant difference.
Sx: Surgery; XRT: Radiotherapy; A: Doxorubicin; CAP: Cyclophosphamide + Doxorubicin + Cisplatin; CT: Chemotherapy
GOG: Gynecologic Oncology Group; JGOG: Japanese Gynecologic Oncology Group; NSGO-EORTC: The Nordic Society of Gynecologic Oncology- European Organization for Research and Treatment of Cancer; MaNGO: Mario Negri Institute.

Table 5. Randomized Controlled Trials of Adjuvant Chemotherapy in Early Stage Endometrial Cancer.

Morrow et al included patients diagnosed with stages IC-IIIC (Morrow et al. 1990). All patients underwent a complete staging followed by the administration of pelvic RT. Patients were then randomized to either doxorubicin (45 mg/m2) or no further treatment. There was no significant difference with regards to either overall survival or progression free survival between the chemotherapy group and the observation group. There was a trend towards fewer extrapelvic recurrences in the doxorubicin arm compared to the control arm (16.3% vs. 22.5%).

In an Italian trial, patients were randomized to either chemotherapy with cyclophosphamide (600 mg/m2), doxorubicin (45 mg/m2), and cisplatin (50 mg/m2) [CAP] or radiation treatment after the initial staging (Maggi et al. 2006). Only one third of the patients in this trial were stage I/II, remaining 2/3 had stage III disease. There was no difference between the CT arm and the RT arm with regards to either overall survival (5year OS: 66% vs. 69%; p=0.78) or progression free survival (5-year PFS: 63% vs. 63%; p=0.45). There were more local recurrences in the CT group compared to the RT group (11% vs. 7%); but distant recurrences were higher in the RT group than the CT group (21% vs. 16%).

In a similar study design; Susumu et al evaluated patients with stages IC-IIIC with > 50% myometrial invasion and no residual tumor after surgery (Susumu et al. 2008). Patients received either pelvic RT (45-50 Gy) or chemotherapy with cyclyophosphamide (333 mg/m2), doxorubicin (40 mg/m2), and cisplatin (50 mg/m2). Patients were divided into low-intermediate risk group (IC plus age <70 years plus grade I/II) and high-intermediate risk group (IC plus age >70 years plus grade III or stage II/IIIA with > 50% myometrial invasion). The 5-year progression free survival for low-intermediate risk patients was 94.5% in the RT group and 87.6% in the CT group (p=0.11). The corresponding 5-year overall survival rates were 95.1% and 90.8%, respectively (p=0.28). The survival was however significantly better in the CT group compared to the RT group among the high-intermediate risk patients (5-year PFS: 83.8% vs. 66.2%, p=0.024; 5-year OS: 89.7% vs. 73.6%, p=0.006). The overall incidence of G3/G4 complications was 1.6% in the RT group and 4.7% in the CT group.

Kuoppala et al randomized high-risk patients after surgery to either radiotherapy alone or radiation plus chemotherapy with cisplatin(50 mg/m2), doxorubicin(60 mg/m2), and cyclophosphamide (500 mg/m2) (Kuoppala et al. 2008). Adjuvant chemotherapy failed to improve overall survival or the recurrence rate in their study [5-year disease specific survival: 84.7% RT vs. 82.1% RT +CT, p=0.148; median disease free survival: 18 months for RT vs. 25 months for RT+ CT, p=0.134).

The Nordic society for gynecologic oncology 9501/ European Organization for Research and Treatment of Cancer Group 55991 and MaNGO/ILIADE-III trial compared radiation alone to radiation followed by CT (Hogberg et al. 2010). The combination of radiation and chemotherapy was associated with a superior progression free survival (HR: 0.63, CI: 0.44-0.89; p=0.009) and cancer specific survival (HR: 0.55, CI: 0.35-0.88; p=0.01) compared to the radiation only arm. Recently, the Cochrane review group led by Johnson et al reported (presented in abstract form at the 2010 annual meeting of the International Gynecological Cancer Society) data from 7 randomized trials and 1,919 women showing a survival advantage in favor of adjuvant chemotherapy (RR: 0.85 CI: 0.75-0.96) (Lai et al. 2011).

While, there is little doubt as to the usefulness of chemotherapy in the treatment of high-risk patients; its role in the treatment of these patients will be further clarified with the results of PORTEC-3 trial (comparing EBRT+CT vs. EBRT alone). It is debatable whether patients receiving adjuvant radiotherapy should receive pelvic RT or vaginal brachytherapy alone. The exclusion of RT in these patients has been shown to increase the risk of pelvic failure in

some studies (Mundt et al. 2001; Klopp et al. 2009). GOG 249 is currently evaluating outcomes in high-intermediate risk and high risk endometrial cancer patients treated with 3 cycles of carboplatin/taxol followed by either VBT or EBRT.

The role of hormone therapy in early stage endometrial cancer has been studied in different randomized trials (Table 6). Only patients with stage I endometrial cancer were included in four trials (Lewis et al. 1974; Malkasian and Bures 1978; Macdonald et al. 1988; De Palo et al. 1993). Other trials also included patients with more advanced disease (COSA-NZ-UK Endometrial Cancer Study Group ; Vergote et al. 1989; Urbanski et al. 1993). A meta-analysis of four of these trials was recently reported by Martin-Hirsch et al. There was no significant difference in the risk of death between patients who received progestogen compared to those who did not receive progestogen (RR: 1.00, CI: 0.85-1.18)(Martin-Hirsch et al. 2011). Although, the risk of relapse was lower in patients receiving progestogen compared to those who did not receive progestogen (RR: 0.71, CI: 0.52-0.97) (Urbanski et al. 1993); this effect was not reproduced in another trial (RR 1.34, CI: 0.79-2.27) (De Palo et al. 1993). The authors concluded that there is no evidence to support the routine use of progestogens in the primary treatment of endometrial cancer.

First Author, yr	N	Stages	Treatment	Risk of Death at 5-yrs Hazard Ratio [95% CI]
1.Lewis et al, 1974	956	I	Progestogen	1.63 [1.00-2.67]
			Control	
2.Malkasian et al, 1978	35	I	Progestogen	1.89[0.40-9.01]
			Control	
3.MacDonald et al, 1988	429	I	Progestogen	1.09 [0.70-1.72]
			Control	
4.Vergote et al, 1989	1048	I-II	Progestogen	1.00 [0.74-1.34]
			Control	
5.Urbanski et al, 1993	205	I-III	Progestogen	0.10 [0.03-0.30][1]
			Control	
6.De Palo et al, 1993	771	I	Progestogen	1.48 [0.82-2.66]
			Control	
7.COSA-NZ-UK, 1998	1012	I-III	Progestogen	0.91 [0.74-1.12]
			Control	

1: Favors progestogen.

Table 6. Randomized Controlled Trials of Adjuvant Hormonal Therapy in Early Stage Endometrial Cancer.
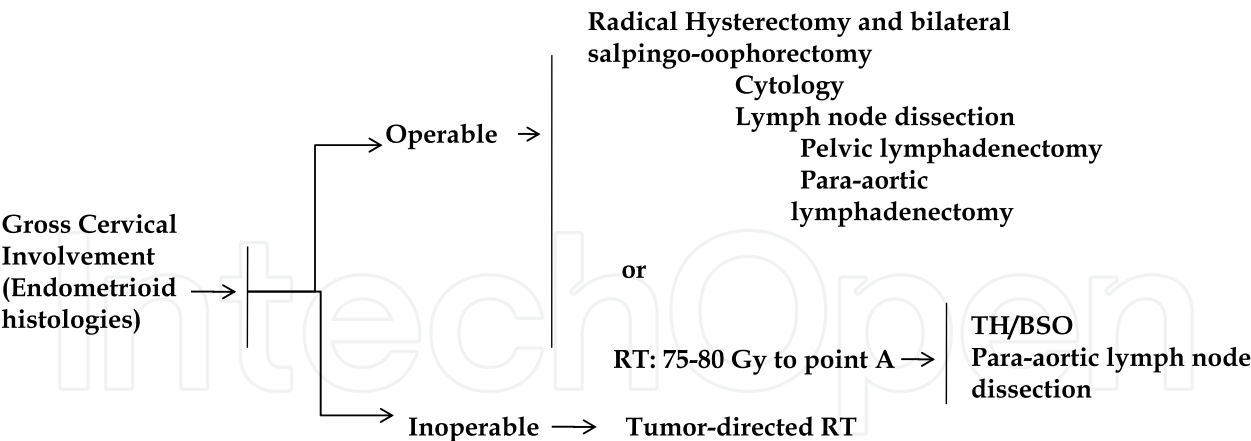
3.2.2 Treatment of endometrial cancer with cervical involvement

In the past, one of the most commonly employed procedure for the treatment of these patients was preoperative RT followed by total abdominal hysterectomy. The 5-year actuarial survival rate reported among patients treated with pre or postoperative radiation therapy has been reported to range from 57% to 85% and 52% to 87%, respectively (Menczer 2005). Calais et al performed a retrospective comparison of outcomes among 184 patients

who received vaginal brachytherapy before or after radical hysterectomy (Calais et al. 1990). There was no significant difference in survival between patients treated with either preoperative or postoperative radiation therapy (87% and 91%, respectively). Similarly, the incidence of local recurrence (13% vs. 9%) and distant recurrence (12% and 9%) was also comparable between the two groups. Although, not statistically significant, a trend towards more late complications was observed in patients treated with preoperative radiation (14% vs. 7.9%). Similar results have been reported by others (Lanciano et al. 1990). Additionally, preoperative RT can confound the pathological determination of grade, depth of myometrial invasion, and pelvic lymph node involvement.

The role of radical hysterectomy in endometrial cancer with cervical involvement has been investigated by several authors. A series by Sartori et al included 203 patients with stage II endometrial cancer (Sartori et al. 2001). Of these; 66% underwent a simple TAH, whereas RH was performed in the remaining 34% patients. The 5-year survival rates were significantly better in the RH group compared to the TAH group (94% vs. 79%, p<0.05). The local and distant recurrences were also fewer in the RH group. Cornelison et al also demonstrated a superior survival among stage II endometrial cancer patients treated with RH compared to TAH (surgery only group: 93% vs. 84%, p<0.05; surgery plus radiation group: 88% vs. 82.7%, p<0.05)(Cornelison et al. 1999).

The schema for risk-stratification for stage II patients and results of clinical trials have been discussed elsewhere in this chapter. The NCCN recommendations for management of this group of patients are as shown in figure 1. Although, both pelvic RT and brachytherapy are recommended; observation or vaginal brachytherapy is also an option for stage II patients who have undergone a RH with negative surgical margins and no evidence of extrauterine disease (NCCN guidelines for uterine neoplams, V.2.2011). In a small study by Ng et al, no recurrences were observed in stage II patients undergoing extended surgical staging followed by vaginal vault brachytherapy (Ng et al. 2001).

Fig. 1. Schematic representation of primary management of endometrial cancer with cervical involvement.

3.2.3 Treatment of advanced stage endometrial carcinoma (stages III and IV)

Although, most endometrial cancers are diagnosed in early stages due to symptoms; those who are diagnosed in advanced stages do poorly on available treatments. Generally, a multimodality approach involving surgery ± radiation ± chemotherapy ± hormonal agents is required. NCCN guidelines for the management of these patients are shown in Figure 2.

Intra-abdominal:
· Ascites
·Omentum
·Nodal
·Ovarian
·Peritoneal

TH/BSO
+ cytology
+ surgical debulking
± pelvic and para-
aortic lymph node
dissection

Extrauterine disease (Endometrioid histologies)

Extrauterine pelvis:
·Vaginal
·Bladder
·Bowel/Rectum
·Parametrial

RT
+ brachytherapy
± chemotherapy
± surgery

Extra-abdominal/liver→

Consider palliative TH/BSO
± chemotherapy
± RT
± hormonal therapy

Fig. 2. Schematic representation of primary management of endometrial cancer with extrauterine disease.

3.2.3.1 Role of cytoreductive surgery

The role of cytoreductive surgery in patients diagnosed with advanced stage endometrial cancer is debatable. Goff et al showed that survival was significantly better in patients that were cytoreduced (18 months) compared to those that did not undergo surgery (8 months) (Goff et al. 1994). In another study, Chi et al compared the outcomes among those stage IV endometrial cancer patients that underwent either optimal cytoreduction (residual disease ≤2 cm), suboptimal cytoreduction (gross residual disease >2cm), or no cytoreduction (Chi et al. 1997). The median survival recorded for patients in these groups was 31 months , 13 months, and 3 months, respectively (p<0.01). Only the extent of cytoreduction was a significant predictor of survival on multivariate analysis. Similar findings have been reported by other investigators (Bristow et al. 2000; Ayhan et al. 2002). Although, data from these small retrospective studies appear encouraging, it is important to note that there has been no randomized trial to date to validate this beneficial effect.

3.2.3.2 Role of radiotherapy

Pelvic radiotherapy with or without vaginal brachytherapy has been used to prevent local and/or lymph node metastasis in patients with advanced stage endometrial cancer. In a study by Mariani et al, the incidence of pelvic side wall recurrences at 5 years was 57% among those node positive stage III/IV endometrial cancer patients that underwent inadequate node dissection and/or no radiotherapy compared to 10% for those receiving both adequate lymphadenectomy and postoperative radiotherapy (p<0.001)(Mariani et al. 2006). While the 5-year para-aortic failure rate was 34% among patients undergoing para-aortic lymphadenectomy and no adjuvant radiation; there were no failures among those 11 patients who received both para-aortic lymphadenectomy and para-aortic radiation. Similarly, in a study, by Mundt et al, there was a trend towards improved local failure rate among those stage IIIC endometrial cancer patients who received vaginal brachytherapy compared to those who did not (vaginal recurrence: 0/10 vs. 4/20; p=0.12)(Mundt et al. 2001).

Due to the risk of abdominal recurrence in advanced stage endometrial cancer and/or high-risk histologies; the use of whole abdominal radiation has been proposed. Smith et al reported a 3-year estimated progression free survival of 79% and overall survival of 89% in 22 patients with stage III/IV adenocarcinoma using postoperative whole abdominal radiation(Smith et al. 2000). All four failures in these patients were extra-abdominal. The 3 year actuarial major complication rate was 7% in their series, and there were no treatment related deaths. In another report by Gibbons et al; the 7-year disease specific survival after WAI was 57.8% for stage III and 25.0% for stage IV disease (p=0.006)(Gibbons et al. 1991). Although, acute toxicity was common, the complications were generally mild.

In the GOG study, the 3-year recurrence free survival was 29% and overall survival was 31% in patients with endometrial adenocarcinoma (Sutton et al. 2005). The corresponding rates in papillary serous/clear cell carcinoma were 27% and 35%, respectively. The incidence of different types of severe toxicities was as follows: myelosuppression (12.6%), gastrointestinal toxicity (15%), and hepatic toxicity (2.2%). Although these results look promising, GOG 122 emphatically established the superiority of chemotherapy over whole abdominal radiation in the treatment of patients with advanced stage endometrial cancer(Randall et al. 2006). The progression free survival and overall survival were both higher in the chemotherapy arm compared to the whole abdominal radiation arm. There were more pelvic failures in the group receiving chemotherapy compared to those treated with WAI (18% vs. 13%). Others have similarly reported high pelvic failure rate with chemotherapy alone (Mundt et al. 2001; Klopp et al. 2009; Barrena Medel et al. 2011). These data lend support to the use of combined modality therapy in the treatment of patients with advanced stage endometrial cancer. Several studies have shown improved outcomes with combination of radiation and chemotherapy (Schorge et al. 1996; Onda et al. 1997; Hoskins et al. 2001; Bruzzone et al. 2004) and it is currently being further evaluated on a Gynecologic Oncology Group study (GOG 258: A Randomized Phase III trial of Cisplatin and Tumor Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked Advanced Endometrial Carcinoma).

3.2.3.3 Role of chemotherapy

In advanced stage endometrial cancer, chemotherapy may be administered in various settings: as primary systemic therapy, adjuvant therapy, or neoadjuvant therapy. Response

rates have been over 20% in phase II studies with anthracyclines, platinum compounds, alkylating agents, and taxanes (Humber et al. 2007). The Gynecologic Oncology Group has undertaken several trials over the last three decades to evaluate the effectiveness of various single agents and combinations in the treatment of advanced/recurrent endometrial cancer (Table 7).

Thigpen et al evaluated those patients with advanced stage (stages III/IV) and recurrent endometrial cancer who were chemonaive and had measurable disease after prior surgery or radiotherapy on GOG 107(Thigpen et al. 2004). A total of 281 patients were eligible. Patients were randomized to receive either doxorubicin alone or a combination of doxorubicin and cisplatin. The overall response rate was significantly higher in the combination arm compared to the doxorubicin alone arm (42% vs. 25%, p=0.004). The median progression free survival was also significantly longer in patients receiving doxorubicin plus cisplatin compared to those who received doxorubicin alone (5.7 months vs. 3.8 months; HR: 0.74 CI: 0.58-0.94). The toxicity was significantly greater in patients treated with the doxorubicin and cisplatin doublet.

Randall et al included patients with stage III/IV endometrial cancer on GOG 122 (Randall et al. 2006). All patients underwent an optimal cytoreduction (residual disease ≤ 2 cm). Patients were then randomized to either whole abdominal irradiation (WAI) or chemotherapy with cisplatin and doxorubicin (AP). Between 1992 and 2000, 422 patients were accrued. The median follow up was 74 months. The 5-year PFS was 50% in the AP arm and 38% in the WAI arm (HR: 0.71 CI: 0.55-0.91, p<0.01). The 5-year overall survival was 55% in the AP arm and 42% in the WAI arm (HR: 0.68 CI: 0.52-0.89, p<0.01). Analysis of the site of recurrence revealed 18% pelvic, 14% abdominal, and 18% extra-abdominal recurrence in the AP arm, and 13% pelvic, 16% abdominal, and 22% extra-abdominal recurrence in the WAI arm. Administration of AP was associated with significantly more acute toxicity (treatment related deaths 4% in AP arm and 2% in the WAI arm).

Homesley et al compared outcomes between stage III/IV endometrial cancer patients treated with combination of cisplatin plus doxorubicin (AP) or cisplatin plus doxorubicin plus taxol (TAP)(Homesley et al. 2009). All patients had previously undergone a cytoreductive surgery followed by tumor volume directed radiation. The 3-year PFS was not significantly different between the two groups (64% vs. 62%; HR: 0.90, CI: 0.69-1.17). Subgroup analysis revealed a significant reduction in the risk of recurrence and death among patients with gross residual disease treated with TAP compared to AP (RR: 0.50, CI: 0.27-0.92). Toxicity was also more frequent and more severe in the TAP arm (p<0.01). Similarly, both median progression free survival (8.3 months vs. 5.3 months; HR: 0.60, CI: 0.46-0.78) and median overall survival (15.3 months vs. 12.3 months; HR: 0.75, CI: 0.57-0.99) were found to be significantly longer in another GOG study among advanced stage patients treated with (TAP) compared to those treated with (AP) (Fleming et al. 2004). Neurotoxicity was worse in the TAP arm compared to the AP arm (40% vs. 5%) and there were 5 treatment related deaths in the TAP arm and none in the AP arm.

The combination of carboplatin and taxol has shown efficacy in phase II setting for the primary treatment of advanced and recurrence endometrial cancer (Hoskins et al. 2001). The 3-year overall survival was 39% and toxicity was acceptable. Many practitioners are already administering this combination despite the lack of evidence from a randomized controlled trial. GOG 209 randomized patients with measurable and non-measurable stage III/IV or

recurrent endometrial cancer to either TAP or carboplatin/Taxol. This trial has finished accrual and its results will be crucial in regards to identifying the most efficacious and safe chemotherapy regimen for treatment of patients with high-risk or advanced endometrial cancer. This combination is also being evaluated in 2 other ongoing GOG trials (GOG 249 and GOG 258, described elsewhere).

First Author, yr (Reference Study)	N	Stages	Regimen	5-yr PFS/ Median PFS	5-yr OS/ Median OS
1. Thigpen et al, 2004	281	III/IV/R	A	3.8 months[1]	9.2 months
(GOG 107)			AP	5.7 months[1]	9.0 months
2. Randall et al, 2006	396	III/IV	AP	50%[1]	55%[1]
(GOG 122)			WAI	38%[1]	42%[1]
3. Fleming et al, 2008	273	III/IV/R	TAP	8.3 months[1]	15.3 months[1]
(GOG 177)			AP	5.3 months[1]	12.3 months[1]
4. Homesley et al, 2009	552	III/IV	Sx + XRT + TAP	64%[2]	---
(GOG 184)			Sx + XRT + AP	62%[2]	---

1: Statistically significant; 2: 3-yr PFS
R: Recurrent; Sx: Surgery; XRT: Radiotherapy; A: Doxorubicin; AP: Doxorubicin + Cisplatin; TAP: Paclitaxel + Doxorubicin + Cisplatin;
GOG: Gynecologic Oncology Group.

Table 7. Randomized Controlled Trials of Adjuvant Chemotherapy in Advanced Endometrial Cancer.

The role of hormonal treatment in advanced endometrial cancer is discussed with recurrent endometrial cancer.

3.3 Papillary serous and clear cell carcinoma

Patients diagnosed with these histotypes should undergo comprehensive surgical staging. In a study by Thomas et al, 52% of patients with clear cell cancer confined to the uterus on clinical assessment were found to have extrauterine disease on surgical staging (Thomas et al. 2008). In another study by Goff et al, high incidence of lymph node metastasis and intraperitoneal metastasis was noted in patients with papillary serous cancer even in the absence of high risk features found significant on GOG 33 (Goff et al. 1994).

Surgical staging should include peritoneal cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, and biopsies of peritoneal surfaces including the underside of diaphragm(NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Uterine Neoplasms V.2.2011. © 2011 National Comprehensive Cancer Network). This is due to the propensity for omental involvement(Sherman et al. 1992; Saygili et al. 2001) and spread to the peritoneal surfaces (Geisler et al. 1999; Chan et al. 2003) in women diagnosed with papillary serous or clear cell

endometrial cancer. Maximum cytoreductive effort is recommended in the presence of extrauterine disease due to the associated survival advantage(Olawaiye and Boruta 2009).

The majority of patients with papillary serous or clear cell cancer relapse outside of pelvis, and distant recurrences are common even in patients with early stage disease. As a result, adjuvant chemotherapy with or without tumor volume directed radiotherapy is widely recommended in all patients, even those in whom the disease is confined to the uterus at the time of diagnosis(NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Uterine Neoplasms V.2.2011. © 2011 National Comprehensive Cancer Network).

3.4 Recurrent endometrial cancer

The risk of endometrial cancer recurrence ranges from 2-15% in early stage disease and 50-60% in advanced stages or aggressive histologies (Salani et al. 2011). The treatment options depend on previous radiation exposure, location and extent of disease, and goals of therapy (curative vs. palliative).

Isolated vaginal recurrence may be treated with surgery, radiotherapy, or a combination of both. For unresectable or disseminated metastases, systemic treatment with hormone therapy, chemotherapy with or without tumor directed radiation is generally employed. Local/regional recurrence can be treated with radiation ± surgical resection in patients with no prior radiation exposure. In the event of prior RT administration, surgical exploration, chemotherapy, or hormonal therapy is preferred (NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Uterine Neoplasms V.2.2011. © 2011 National Comprehensive Cancer Network). An analysis of survival after relapse in patients included in the PORTEC-trial, revealed 3-year survival rates of 73% after vaginal relapse, 8% after pelvic relapse, and 14% after distant relapse. There was no significant difference in survival between patients with pelvic and distant relapse (Creutzberg et al. 2003).

Historically, total pelvic exenteration has been performed in select patients who have failed the standard surgery and radiation treatment with reported long term survival rates of 20-45% and complication rates of 60-80% (Morris et al. 1996; Barakat et al. 1999). For patients who are not candidates for pelvic exenteration, the existing options are not very effective. In order to enhance the response to salvage therapies; the role of cytoreductive surgery has been explored. Scarabelli et al reported a complete macroscopic resection of disease in 65% patients with recurrent endometrial cancer, with significant improvement in survival (p<0.01)(Scarabelli et al. 1998). In another series by Bristow et al, 61 patients with recurrent endometrial cancer were evaluated (Bristow et al. 2006). The median post recurrence survival was significantly longer in the optimally cytoreduced patients compared to those left with gross residual disease (39 months vs. 14 months, p=0.0005). Similar results have been reported by others (Campagnutta et al. 2004; Awtrey et al. 2006).

Hormonal agents have been found valuable in patients with advanced/recurrent disease. They are generally associated with fewer side effects (compared to systemic chemotherapy) making them particularly suitable for use in patients with poor performance status and/or multiple co-morbidities. Various hormonal agents have been used (progestins, selective estrogen receptor modulators, aromatase inhibitors, synthetic steroid derivatives, and gonadotropin-releasing (GN-RH) hormone analogs) with a response rate of 9% to 55% in different studies(Kokka et al. 2010). Cochrane Database Systematic Review of hormonal

therapy in advanced or recurrent endometrial cancer assessed 542 patients from 6 different randomized trials(Stolyarova I ; Rendina et al. 1984; Ayoub et al. 1988; Urbanski et al. 1993; Thigpen et al. 1999; Pandya et al. 2001) (Table 8). The results indicated that hormonal therapy did not prolong overall survival or progression free survival in women with advanced or recurrent endometrial cancer (Kokka et al. 2010). Low-dose hormonal therapy was more effective than high-dose hormonal therapy (Thigpen et al. 1999). Despite the lack of survival advantage, hormonal agents may be used to alleviate symptoms and prevent progression.

First Author, yr	N	Stages	Treatment	Risk of Death or Recurrence Hazard Ratio [95% CI]
1.Rendina et al, 1984	93	III/IV	TMX MPA	1.00 [0.77-1.29]
2. Ayoub et al, 1988	43	IV/R	CAF CAF + MPA + TMX	0.80 [0.48-1.33]
3. Urbanski et al, 1993	31[1]	III	Progestogen Control	0.08 [0.01-1.28]
4. Thigpen et al, 1999	299	III/IV/R	MPA (200 mg/day) MPA (1000 mg/day)	1.31 [1.04-1.66]
5. Stolyarova et al, 2001	14[1]	III	XRT XRT + OPC	1.00 [0.40-2.48][2]
6. Pandya et al, 2001	62	III/IV	Megestrol Megestrol + TMX	1.03 [0.87-1.22]

1: Sub-group analysis; 2: Risk of recurrence
R: Recurrent
TMX: Tamoxifen; MPA:Medroxyprogesterone Acetate; CAF: Cyclophosphamide + Adriamycin + 5-Fluorouracil; XRT: Radiotherapy; OPC : 17-Oxyprogesterone Caproate.

Table 8. Randomized Controlled Trials of Adjuvant Hormonal Therapy in Advanced Endometrial Cancer.

4. Post treatment surveillance

The current NCCN guidelines recommend physical examination every 3-6 months for 2 years and then 6 months or annually thereafter(NCCN Clinical Practice Guidelines in

Oncology (NCCN Guidelines™) for Uterine Neoplasms V.2.2011. © 2011 National Comprehensive Cancer Network). A review of symptoms and physical examination is recommended at each visit. The yield of vaginal cytology (0-7%) and CXR (0-20%)for detection of recurrence has been shown to be very low in asymptomatic patients and therefore not currently recommended for routine use(Salani et al. 2011). Although, monitoring CA-125 levels may be beneficial in select patients (advanced stage disease, serous histology, pretreatment elevated CA-125); its routine use is also not supported by the available evidence (Salani et al. 2011).

5. Prognosis

The data concerning survival are provided in the Annual Report on the Results of Treatment in Gynecological Cancer (Creasman et al. 2006)and are shown in Table 9.

Strata	Patients	1-Year OS	3-Year OS	5-Year OS
Stage IA	1,054	98.2%	95.3%	90.8%
Stage IB	2,833	98.7%	94.6%	91.1%
Stage IC	1,426	97.5%	89.7%	85.4%
Stage IIA	430	95.2%	89.0%	83.3%
Stage IIB	543	93.5%	80.3%	74.2%
Stage IIIA	612	89.0%	73.3%	66.2%
Stage IIIB	80	73.5%	56.7%	49.9%
Stage IIIC	356	89.9%	66.3%	57.3%
Stage IVA	49	63.4%	34.4%	25.5%
Stage IVB	206	59.5%	29.0%	20.1%

Data taken from Creasman et al, 2006.

Table 9. Carcinoma of the Corpus Uteri: Patients Treated from 1999-2001; Survival Rates by FIGO Surgical Stage.

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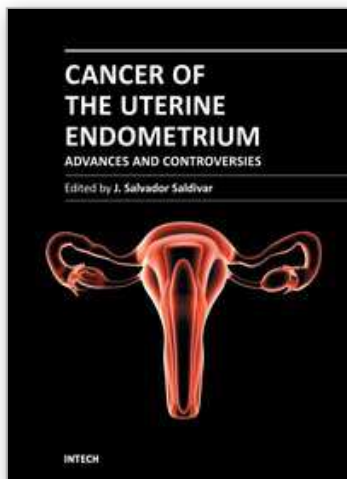
The book Cancer of the Uterine Endometrium - Advances and Controversies brings together an international collaboration of authors who share their contributions for the management of endometrial carcinoma. The scope of the text is not basic, but rather aims to provide a comprehensive and updated source 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.

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