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Prevention and Therapeutic Strategies in Endometrial Cancer

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1. Introduction

Endometrial cancer is the most common gynecological cancer in developed countries. Endometrial cancer primarily affects postmenopausal women, with a median age at diagnosis of 60 years approximately 25% of women are premenopausal at diagnosis and up to 5% of these are below the age of 40 years [Orr, 1997].

2. Clinico-anatomopathological characteristics

17 studies covering 10,572 women showed a prevalence of a malignancy within endometrial polyps in postmenopausal women about 5.42% compared to 1.70% in premenopausal women [Lee, 2010]. Endometrial neoplasia was identified in 214 of 3,946 women with endometrial polyps who were postmenopausal compared with 68 of 3,997 premenopausal women (relative risk 3.86). There were 4,967 women with symptomatic bleeding and 195 from them (4.15%) had neoplastic polyps compared with 85 of 3,941 (2.16%) without normal bleeding, according to the report (relative risk 1.97). Looking at the increased risks seen with postmenopausal status and abnormal bleeding, this did not seem to be additive. Polyp size did not appear to be associated with malignancy. Women with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome have a markedly increased risk of endometrial cancer compared with women in the general population. Among women who are HNPCC mutation carriers, the estimated cumulative incidence of endometrial cancer ranges from 20% to 60% [Morrow, 1991; Goff, 1994]. In terms of histopathology, endometrial cancer can be considered as two types: type I, endometrioid, most commonly seen in 80-90% of cases and type II, and all other forms nonendometrioide serous. Endometrial carcinoma has three architectural degrees, depending on Solid to glandular component rate (for grade 1 is <5% and >50% for grade 3). That tipycally will be arised in younger obese women, hyper lipidemia, and signs of hyperestrogenism (exogenous or endogenous). Serous carcinomas are high-grade carcinomas. Comprising -1% of endometrial adenocarcinomas, the clear cell carcinomas are rare. There is an increasing of them in thinner, older women and show no hormonal risk factors. The endometrial carcinomas type I are commonly diagnosed at an early stage and have a favorable prognosis, often only surgically treated; recurrences are usually local (the most common site is pelvis) and curable very frequently with tumor-

directed radiotherapy. The carcinomas type II from endometrial are present with metastatic disease at diagnosis and carry a poorer prognosis (Soslow 2007). Complex or simple hyperplasia could be associated with cellular atypia. We can subdivide them into mild atypia (nuclear enlargement and rounding with evenly dispersed chromatin) or moderate atypia (clumped chromatin, larger nuclear size, prominent nucleoli). There is a low likelihood of hyperplasia without atypia, either simple or complex (1%, 3%) of progressing to carcinoma. In contrast, atypical endometrial hyperplasia is believed to be the direct precursor to endometrioid carcinoma [Bokhman, 1983; Soslow, 1997]. An investigation by The Gynecologic Oncology Group found that from19% to 62% of endometrial biopsy. There is an association between endometrial hyperplasia and invasive endometrial cancer postoperative. (Merisio, 2005) Complex and simple hyperplasia can be treated with only progestative therapy, whereas hysterectomy is mandatory for patients with atypical hyperplasia. Atypical hyperplasia regresses after treatment with progestational therapy in 60% to 95% of patients [Randall, 1997].

In patients with atypical hyperplasia and the high risk of progression to endometrium carcinoma, hysterectomy is the standard treatment. For women who desire a fertility preserving therapy should be reserved progestative therapy for six months (Trimble, 2006).

The risk factors of endometrioid cancer are late menopause, continuous anovulation (e.g., polycystic ovarian syndrome), obesity and nulliparity. Additional risk factors may be related to estrogenic effects, a high-fat diet, tamoxifen use, early menarche. Endometrioid adenocarcinomas frequently show genetic instability, typically found in patients with hereditary nonpolyposis colon cancer and mutations (the b-catenin gene is more frequently mutated in carcinomas with squamous differentiation). Serous carcinomas are characterized by chromosomal instability and p53 mutations. Clear cell carcinomas have absent reactivity for estrogen and progesterone receptors and low immunoreactivity for p53. After an initial assessment, necessary treatment of the disease, this depends on its stage of development and disease risk (the risk of recurrence and metastasis).

2.1 Assessment

Assessment of myometrial invasion is to specify the page, the possible extension to the pelvic organs and distance and tumor grade. This evaluation consisted of noninvasive preoperative investigations (imaging) and invasive (biopsy curettage). CT scans have poor sensitivity and specificity in detecting the depth of myometrial invasion, cervical and parametrial involvement, and lymph node metastases [Zerbe, 2000]. MRI appears to be the best imaging modality for preoperative assessment of myoinvasion [Kinkel, 2009]. MRI presents an overall staging accuracy of 85% [Hricak, 1991]. In addition, whilst more accurate than CT, the limitations of MRI in detecting myometrial invasion must be considered [Kinkel, 1999]. In one institutional review of endometrial cancer, 30% of tumors were found to be at an advanced stage and 24% of women had high-grade tumors [Bandyopadhyay, 2008]. Another study of 301 women with stage I endometrial cancer reported that the negative predictive value of MRI for myometrial invasion was 49.2% [Suh, 2009]. The use of PET/ CT is reported in small prospective series to have a high negative predictive value for nodal metastases [Frumovitz, 2004; Signorelli, 2009; Picchio, 2010]. Park demonstrated that PET/CT had a sensitivity of 69.2%, specificity of 90.3%, positive predictive value of 42.9%, and negative predictive value of 96.6 % [Park, 2008].

Endometrial cancer is generally staged according to the International Federation of Gynecology and Obstetrics (FIGO) system. Since 1988, the FIGO system has recommended surgical staging with systematic pelvic and para-aortic lymphadenectomy. In May 2009, a new FIGO staging system was published, but most of studies are based on the old classification (Tables 1). Some centers use intraoperative frozen section analysis of the uterus based upon histological grade, type and depth of myometrial invasion and appears significantly better than MRI scanning in the assessment of myometrial invasion. [Furukawa, 2010].

Stage	Involvement
Stage I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus Endocervical glandular involvement alone should be considered as stage I
Stage III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae†
IIIB	Vaginal and/or parametrial involvement†
IIIC	Metastases to pelvic and/or para-aortic lymph nodes†
IIIC 1	Positive pelvic nodes
IIIC 2	Positive para-aortic lymph nodes ± positive pelvic lymph nodes
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases ± inguinal nodes

*Positive cytology should be reported separately without changing the stage [Pecorelli, 2009].

Table 1. FIGO staging of endometrial cancer

2.2 Risk assessment

Multiple factors have been identified for relative high risk of recurrence in apparent early-stage disease: histological subtype, grade 3 histology, myometrial invasion ‡50%, lymphovascular space invasion (LVSI), lymph node metastases and tumor diameter >2 cm.

Stage I can be subdivided into three risk categories [Fiorelli, 2008]:

Low risk:	stage IA (G1 and G2) with endometrioid type
Intermediate risk:	stage IA (G3) with endometrioid type
	stage IB (G1 and G2) with endometrioid type
High risk:	stage IB (G3) with endometrioid type
	all stages with non-endometrioid type

2.3 Surgical staging

Full staging endometrial cancer can be performed surgically [Pecorelli, 2009]. In addition to data related to uterine tumor, surgical research can provide data about state and pelvic lymph lomboaortic by lymphadenectomy. Studies of women undergoing full pelvic

lymphadenectomy report rates of occult pelvic lymph node disease ranging from 8 to 28% depending on grade and depth of myometrial invasion [Zivanovic, 2009; Lin, 2008]. Lymphadenectomy causes significant morbidity in approximately 11% of cases [Nunns, 2000]. Pelvic MRI and sentinel lymph node evaluation appear equally effective in detecting pelvic node metastases although the ability to detect the sentinel node varies significantly between studies [Selman, 2008]. Hirahatake reported that para-aortic lymph node metastases in 2.5% of stage IA, 8.5% of stage IB, and 15.7% of stage II endometrial cancers [Hirahatake, 1997]. Mariani and Tanaka reported a direct correlation between pelvic and para-aortic lymph node involvement [Mariani, 2004; Tanaka, 2006]. In a study of 291 endometrial cancer patients by Goudge 18% were upgraded postoperative [Goudge, 2004]. Ben-Shachar reported that tumor was upgraded in 19% of 181 patients with a preoperative grade 1 tumor [Ben-Shachar, 2005]. The results of surgical staging also led to adjuvant treatment in 12% of patients who were found to have extrauterine disease or other high-risk characteristics [Ben-Shachar, 2005].

3. Prevention

Pain was the most common complain in patients with recurrent disease, in the follow-up of endometrial cancer patients, followed by vaginal bleeding, general malaise, loss of weight and intestinal complaints (Zhang, 2010). The routine use of the Pap smear and systematic radiography are not clinically justified in the follow-up of patients with endometrial carcinoma (Agboola, 1997; Morice, 2001). In Lynch syndrome, the current gynecologic carcinoma screening guidelines include annual endometrial sampling and transvaginal ultrasonography beginning at age 30-35 years (178). Primary prevention by using a progesterone device in utero, such as the Mirena IUCD is an alternative approach. This merits full evaluation (Hitchener, 2006). Prophylactic hysterectomy and bilateral salpingoophorectomy should be offered as risk-reducing surgery to women aged 35 years or older who do not wish to preserve fertility. Schmeler et al. reported a retrospective analysis with known germ line mutations associated with Lynch syndrome. There were sixty-one participants who underwent prophylactic hysterectomy and were compared to over 200 matched controls with similar mutations that did not have preventive surgery. In 33% of the controls was eventually diagnosed the endometrial cancer, with no cases in the prophylactic group (Schmeler, 2006). There was detected asymptomatic muscle invasive endometrial carcinoma by Pistorius et al, in two of four women who underwent prophylactic hysterectomy after requiring surgery for Lynch syndrome related colorectal carcinoma (Schmeler, 2006). In 2006, a multiinstitutional, matched case-control study found that prophylactic bilateral salpingoophorectomy and hysterectomy preventive strategy in women with HNPCC syndrome [Schmeler, 2006]. Most cases of endometrial cancer cannot be prevented, but women can take some measures to reduce their risk of developing endometrial cancer. Risks might be reduced with using oral contraceptives controlling obesity and controlling diabetes.

In addition, women who are considering estrogen replacement therapy should talk to their doctors to assess their risk of endometrial cancer. Use of combination oral contraceptives (birth control pills) decreases the risk of developing endometrial cancer.

Women who use oral contraceptives at some time have half the risk of developing endometrial cancer as women who have never used oral contraceptives.

This protection occurs in women who have used oral contraceptives for at least 12 months, and continues for at least 10 years after oral contraceptive use. The protection is most notable for women who have never been pregnant.

Edward Giovannucci, M.D., Sc.D., Professor of Nutrition and Epidemiology at the Harvard School of Public Health, said coffee is emerging as a protective agent in cancers that are linked to obesity, estrogen and insulin. Giovannucci, along with Youjin Je, a doctoral candidate in his lab, and colleagues observed cumulative coffee intake in relation to endometrial cancer in 67,470 women who enrolled in the Nurses' Health Study. During the course of 26 years of follow-up, researchers documented 672 cases of endometrial cancer. Drinking more than four cups of coffee per day was linked with a 25 percent reduced risk for endometrial cancer. Drinking between two and three cups per day was linked with a 7 percent reduced risk [Giovannucci, 2005]. A similar link was seen in decaffeinated coffee, where drinking more than two cups per day was linked with a 22 percent reduced risk for endometrial cancer.

Hormone and lifestyle factors explain up to 80% of risk for endometrial cancer. The investigators found that women who were normal weight and active had a reduction in risk of 73%, compared with inactive women who were overweight (BMI above 25 kg/m^2). Women who were normal weight but inactive had a 55% lower risk for endometrial cancer than inactive women who were overweight. Women who were overweight but active had a 38% lower risk for endometrial cancer.

Aspirin has been shown in vitro to inhibit endometrial cancer cell growth through the induction of apoptosis in a dose-dependent manner [Arango, 2001].

Other NSAIDs have also been shown to reduce endometrial cancer cell proliferation and induce apoptosis in a dose- and time-dependent manner [Gao, 2004; Li, 2002].

African-american women with advanced stage endometrial cancer have lower survival rates than white women with the disease even when both groups receive similar treatments, according to a study published online September 25, 2006, in the journal Cancer .

4. Therapeutic strategies

4.1 Molecularly targeted treatments

One of the major challenges in endometrial cancer treatment remains the current inability to effectively prevent distant metastasis in women with deeply myoinvasive, high-grade or biologically aggressive tumors (e.g., serous and clear cell cancers). One potential target in serous tumors is HER_2 [Konecny, 2009; Villella, 2006; Flemimg, 2003]. The monoclonal antibody trastuzumab binds to HER-2 and can reduce growth in cell lines that overexpress HER-2. Epidermal growth factor receptor (also known as c-erbB-1). One strategy to tackle tumor growth is to target angiogenesis,. The main factor controlling angiogenesis is VEGF. The most well known of these is bevacizumab, a monoclonal antibody against VEGF-A. A study of single-agent bevacizumab in women with recurrent endometrial cancer demonstrated a 15% response rate and a median progression-free survival of 4 months, although approximately 36% of women had a progression-free survival of 6 months [Konecny, 2009].

A number of other antiangiogenic agents are currently being tested as single agents in Phase II trials. These include VEGF–Trap and small-molecule inhibitors of VEGF receptors [Hayes, 2009; Hayes, 2010].

One of the main challenges will be getting the more promising drugs into the clinic. Development of these newer drugs is expensive and costs will therefore be high. Whether there is a therapeutic role for lymphadenectomy in nonendometrioid tumors remains an unanswered. It has been possible to provide clear guidance with respect to the use of radiotherapy following the completion and publication of several key trials in this area, and treatment is now applied on an individualized patient basis. The investigators found that women who were normal weight and active had a reduction in risk of 73%, compared with inactive women who were overweight (BMI above 25 kg/m^2). Women who were normal weight but inactive had a 55% lower risk for endometrial cancer than inactive women who were overweight. Women who were overweight but active had a 38% lower risk for endometrial cancer.

4.2 Treatment of localized disease

In the case of a low-risk disease evolution, with tumor confined to the uterus, non-aggressive treatment is required, while high-risk disease require evolution untreatment multimodal radiochimiotherapy. Treatment of localized disease is mainly surgical and consists of a total hysterectomy with bilateral anexectomy as or no lymphadenectomy. The problem is the continuing debate and systematic lombo-aortic lymphadenectomy role. Lymphadenectomy can be selectively performed in women at highest risk of nodal metastases (deeply invasive or high-grade tumors) [Mariani, 2008]. Lymphadenectomy causes morbidity in approximately 11% of cases [Nunns, 2000]. In an effort to decrease the morbidity that results from lymphadenectomy, the sentinel node approach has been successfully employed. If the sentinel node is pathologically negative for metastasis, all downstream nodes should also be negative and would not require dissection. This technique yielded an overall detection rate of 82%-89% [Niikura, 2004; Delaloye, 2007]. Presently the sentinel lymph node biopsy in endometrial cancer is still an investigational technique. Studies of women undergoing full pelvic lymphadenectomy report rates of occult pelvic lymph node disease ranging from 8 to 28% depending on grade and depth of myometrial invasion [Creasman, 1987; Chi, 2008]. At present there is great uncertainty regarding what is the optimal adjuvant treatment for localized endometrial cancer. The use of adjuvant therapy for endometrial cancer depends on the patient's estimated risk of recurrence. Novel techniques for the delivery of radiation, including intensity-modulated radiation therapy and tomotherapy are promising technologies to improve the therapeutic index for patients receiving combined therapy [Lian, 2008; Salama, 2006; Beriwal, 2006]. A number of trials are ongoing to examine novel biologic and target therapies for women with endometrial cancer [Konecny, 2008; Kamat, 2007; Wright, 2007; Ozbudak, 2008; Morrison, 2006]. Systemic treatment for metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy.

4.3 Surgical treatment

The surgical approach for the treatment of endometrial cancer has traditionally been laparotomy. In the last years, the use of minimally invasive techniques is widely accepted

by many authors. A recent publication of the GOG LAP2 study has shown similar operative outcomes in the minimally invasive surgery group [Walker, 2010]. Authors have reported that the economic benefits of laparoscopy [Scribner, 1999]. Laparoscopy seems to provide equivalent results in terms of disease-free survival and overall survival compared with laparatomy, with further benefit: shorter hospital stay, less use of pain killers, lower rate of complications and improved quality of life. An increasing number of studies have shown no difference in survival or recurrence between laparoscopy and laparatomy surgery, in early- and advanced-stage endometrial cancer [Eltabbakh, 2002; Holub, 2002; Nezhat, 2008]. Recent reports have examined robotically assisted hysterectomy in the treatment of gynecologic malignancies [Advincula, 2006]. The robotic approach could be a 'benefit' in obese women. (Boggess, 2008], but access to the high para-aortic area appears to be limited compared with the laparoscopic or open surgical approaches [Soliman, 2010]. When surgery is not feasible due to medical contraindications (5–10% of patients), external radiation therapy with or without intracavitary brachytherapy to the uterus and vagina is suitable for individual clinical use [Colombo, 2011]. In three trials women treated with laparoscopic hysterectomy were compared with 193 women treated with open surgery and there appears to be no significant difference in either disease-free or overall survival [Lin, 2008; Palomba, 2009].

4.4 Surgical treatment in stage I endometrial cancer

The standard surgical treatment for stage I endometrial cancer is radical hysterectomy and bilateral anexectomy with or without lymphadenectomy. In young women with stage IA endometrial carcinoma is proposed to preserve fertility, based on the hysteroscopic resection of the tumor followed by hormone therapy regimen of megestrol acetate (160 mg/day) [Mazzon, 2010]. The role of systematic pelvic lymphadenectomy is in current debate. Mariani states that patients with stage I endometrial cancer, excluding stage IA–IB G1, systematic lymphadenectomy did not improve disease-free or overall survival [Mariani 2000]. In the ASTEC randomized trial, women with endometrial cancer confined to the uterus and pelvic lymphadenectomy was no evidence of benefit on overall survival or recurrence-free survival [Blake, 2009]. The authors recommended that systematic pelvic lymphadenectomy cannot be recommended in women with stage I endometrial cancer. Lymphadenectomy is highly important for determining a prognosis and in tailoring adjuvant therapies. Prognostic factors for para-aortic spread are similar to those for pelvic nodal disease and include depth of myometrial invasion and the presence of lymphovascular space invasion [Fotopoulou, 2010; Park, 2010; Nomura, 2006]. Many authors suggest a lymphadenectomy for intermediate–high risk endometrial cancer (stage IA G3 and IB) [Colombo, 2011]. Lymph node sampling did not appear to confer a survival benefit in patients with stage IA, grade 1 or 2 tumors, but improved survival in patients with grade 3 [Trimble, 1998]. External beam radiation has been shown to reduce the rate of locoregional recurrence in intermediate-risk endometrial cancer. The Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) trial randomly assigned 715 women with endometrial cancer stage IB grade 2-3 tumors or stage IC grade 1-2 tumors who underwent surgery treatment to whole pelvic radiotherapy versus no further treatment. After 10 years of follow-up there was a reduction in vaginal recurrences from 15 to 4% but no difference in survival [Creutzberg, 2000]. Aalders and collaborators published the results of 540 women with stage I endometrial cancer that underwent surgical treatment and

vaginal brachytherapy and were randomized to whole pelvic radiation versus observation. Pelvic control was improved with the addition of radiotherapy, but there were no survival differences at 5 years [Aalders, 1980]. Nout publish the results of a randomized clinical trial (PORTEC-2) comparing vaginal brachytherapy and external beam radiation in intermediate-risk patients [Nout, 2010]. This study showed no any difference in overall survival or progression-free survival (PFS). The quality of life was better in the vaginal brachytherapy treatment. Radiation of patients who underwent hysterectomy with comprehensive lymphadenectomy improves local control and disease-free survival, but did not affect overall survival. (Keys, 2004) but is associated with appreciable toxicity [Creutzberg, 2000; Keys, 2004]. ESMO Guidelines Working Group 2011 recommended in stage IB G1-2 with negative prognostic factors pelvic radiotherapy and/or adjunctive chemotherapy could be considered [Colombo, 2011]. Endometrial cancer stage I with grade 3 tumors combination chemotherapy to pelvic radiotherapy require. Platinum-based chemotherapy can be considered in stage I G3 with adverse risk factors (patient age, lymphovascular space invasion and high tumor volume) platinum-based adjuvant chemotherapy for early (stage I) disease improves PFS and overall survival. Two trials, one Italian and one Japanese in high-risk patients comparing five courses of cisplatin, doxorubicin and cyclophosphamide with external pelvic radiation reported no difference between therapies in terms of PFS or overall survival [Maggi, 2006; Susumu, 2008]. Chemotherapy appeared superior to pelvic radiotherapy in patients with stage IC, aged >70 years with outer half myometrial invasion, with grade 3, or with stage I disease and positive peritoneal cytology [Maggi, 2006]. In a Cochrane Collaboration review of adjuvant radiotherapy for stage I, external-beam radiotherapy resulted in a 72% reduction in pelvic relapses, a reduction in death in patients with multiple high-risk factors (stage IC and grade 3 tumors) did not translate into a reduction in distant metastatic [Kong, 2007].

4.5 Surgical treatment in stage II endometrial cancer

Traditionally, the surgical approach consists of radical hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without paraaortic lymphadenectomy. In stage II, lymphadenectomy is essential to guide surgical staging and adjuvant therapy. Para-aortic dissection should aim to remove the nodes to level of the mesenteric artery up to the renal vessels, rather than restricting dissection to the level of the inferior mesenteric artery. Large retrospective nonrandomized studies demonstrated that women, who have a para-aortic dissection, have improved outcomes, with increased overall survival [Chan, 2006; Chan, 2007]. Authors show that women at intermediate or high risk of disease recurrence should have pelvic and para-aortic lymphadenectomy and no benefit was seen in low-risk patients [Todo, 2010]. ESMO suggests that adjuvant treatment in stage II consists of pelvic radiotherapy and vaginal brachytherapy. If prognostic factors (grade 1–2 tumor, myometrial invasion <50%, LVSI and complete surgical staging) are negative-brachytherapy alone. If prognostic factors are negative it is feasible chemotherapy with/without radiation [Colombo, 2011].

Chemotherapy appeared superior to pelvic radiotherapy in patients with stage II with a significantly higher overall survival and progression-free survival and the rate of pelvic recurrence was the same (7%). (Susumu, 2008) Platinum-based chemotherapy can be considered in this stage. In retrospective series that platinum-based adjuvant chemotherapy for stage II disease improves PFS and overall survival [Soliman, 2010].

4.6 Surgical treatment in stage III-IV endometrial cancer

Maximal surgical debunking is imperative in patients with a good performance status. The surgical approach consists of anterior and posterior pelvic exenteration. For distant metastatic disease, palliative surgery could be considered in patients with a good performance. If positive nodes: radiotherapy. If metastatic disease: chemotherapy–radiotherapy for palliative treatment [Colombo, 2011]. Traditionally, treatment for women with stage III endometrial cancer has relied on radiotherapy while women with stage IV disease have been treated with palliative chemotherapy [Ross, 2008; Denschlag, 2007; Mariani, 2006]. 396 women with stage III or IV disease were randomized to postoperative whole abdominal radiation versus chemotherapy with doxorubicin and cisplatin. Patients in the chemotherapy group had a statistically significant increased progression-free (42 vs 38%) and overall survival (53 vs 42%) [Gallion, 2003]. Agents for endometrial cancer appear to be doxorubicin and cisplatin. Response rates to single-agent doxorubicin alone are generally in the range of 17-25% [Carey, 2006; Gallion, 2003]. Two prospective randomized trials have demonstrated a superior response rate to doxorubicin and cisplatin as compared with doxorubicin alone, however, with similar survival rates [Thigpen, 1994; Thigpen, 2004, Aapro, 2003]. When carboplatin is associated with cisplatin, is reported a response rate of greater than 40% [Akram, 2005; Dimopoulos, 2000; Sovak, 2006; Secord, 2007]. Given this provocative data, doxorubicin plus paclitaxel was investigated by the GOG (GOG 163) as an alternative to doxorubicin and cisplatin for women with advanced or recurrent disease. Doxorubicin, cisplatin and paclitaxel demonstrated a significant improvement in response rate, progression free and overall survival, but toxicity was much higher with the three drug regimen [Fleming, 2004]. The combination with cisplatin and doxorubicin or cisplatin, doxorubicin and paclitaxel for women with stage III and IV completely resected endometrial cancer appeared equivalent [Alvarez, 2007; Bruzzone, 2004]. Patients with stage IIIC underwent adjuvant treatment with paclitaxel and concurrent pelvic radiation therapy. Overall survival was 81% at 3 years with a median time to relapse of 19 months [Mangili, 2006]. In a similar design, Greven and colleagues reported on 46 patients with endometrial adenocarcinoma with greater than 50% myometrial invasion, stromal invasion of the cervix, or extrauterine disease confined to the pelvis and/or positive peritoneal cytology that underwent postoperative adjuvant treatment with pelvic radiation therapy, vaginal brachytherapy and concurrent cisplatin and paclitaxel. Survival at 4 years was 85% [Greven, 2006].

4.7 Locoregional recurrence

Radiation therapy is standard treatment for vaginal recurrence (external beam plus vaginal brachytherapy). There is high rates in local control, complete response (CR) and 5-year survival is 50%. Surgery is the treatment of choice for pelvic recurrence, or radiation therapy, while for regional pelvic recurrences it is radiation therapy, associated if possible with chemotherapy.

The combination of Doxorubicin, Cisplatin, and Paclitaxel was found to produce an improvement in progression free survival for patients with recurrent endometrial cancer, compared with the two drug combination of Doxorubicin and Cisplatin [Fleming, 2000]. When using adjuvant chemotherapy without adjuvant radiation therapy in patients with advanced-stage endometrial cancer, 40% of women experienced a pelvic relapse at 3 years

[Mundt, 2001]. Five year local control rate of 54%, disease specific survival of 51%, and overall survival of 44% has been reported in a group of patients with locoregional recurrence who made radiotherapy alone [Sears, 1994]. The tumors tend to become resistant to progestational therapy, but may offer a prolonged complete response interval [Fiorica, 2000]. For first-line chemotherapy combinations regimens are preffered of recurrent endometrial cancer.

4.8 Advanced disease

There is no agreement on the standard treatment for women with advanced endometrial cancer. A combination of optimally debulked, radiotherapy and chemotherapy is employed. Metastatic endometrial cancer can be effectively treated with progestational agents. Response rates ranged from 40% with grade 1 disease and 0% with Broder's grade 4 lesions. [Podratz, 1985]. ESMO recommended hormonal therapy for endometrioid histologies only with overall response 25% [Colombo, 2011]. Chemotherapy alone determines a response rate of 40%. The most commonly used are compounds, antracyclines and taxanes, alone and in combination. Paclitaxel-based combination regimens are preffered for first-line chemotherapy of advanced endometrial cancer. The consistent response rate was only for paclitaxel>20% [Colombo, 2011]. The paclitaxel-containing regimens demonstrated a response rate > 60% and a possibly prolonged survival. GOG shows that patients with metastatic endometrial carcinoma require pelvic irradiation with or without paraaortic irradiation, followed by cisplatin, doxorubicin and paclitaxel (Randall, 2006).

4.9 Papillary serous carcinoma and clear cell carcinoma

Papillary serous and clear cell carcinoma require total hysterectomy, bilateral salpingoophorectomy, pelvic and paraaortic lymphadenectomy, omentectomy, appendectomy and peritoneal biopsies. There is more aggressiveness with higher rates of metastatic disease and lower 5-year survival rates. The same chemotherapy regimens usually used for ovarian cancer could be also used in women with advanced or recurrent papillary serous or clear cell uterine cancer. Papillary serous endometrial carcinomas have not been considered to be hormone responsive [Colombo, 2011].

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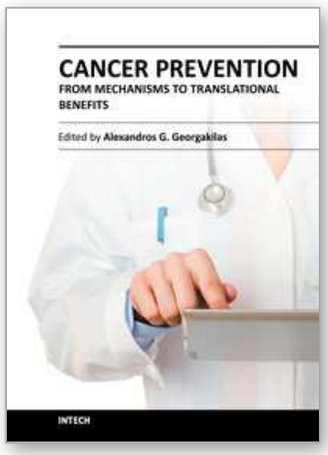

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This unique synthesis of chapters from top experts in their fields targets the unique and significant area of cancer prevention for different types of cancers. Perspective readers are invited to go through novel ideas and current developments in the field of molecular mechanisms for cancer prevention, epidemiological studies, antioxidant therapies and diets, as well as clinical aspects and new advances in prognosis and avoidance of cancer. The primary target audience for the book includes PhD students, researchers, biologists, medical doctors and professionals who are interested in mechanistic studies on cancer prevention and translational benefits for optimized cancer treatment.

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