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What is new in endometrial cancer treatment?

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Endometrial cancer (EC) is the second most common malignancy of the female reproductive system worldwide [1]. It is more prevalent in developed regions (North America, Europe, Australia and New Zealand), compared with less developed ones (Central and South America, Asia and Africa) [1]. The disease usually affects postmenopausal women and the average annual incidence is about 2.1% [1]. Most patients have abnormal uterine bleeding, as the main presenting symptom [1].

Classification of sporadic EC in 2 different types based on clinical and pathological features, is widely acceptable and plays an important role in patient management [2]. These 2 types have distinct etiology, natural history and clinical behavior [2]. More specifically, type I EC is more common (70-80% of sporadic cases) and endometrioid in histology, has a less aggressive clinical behavior and a more favorable prognosis [2]. In contrast, type II EC is less common (10-20% of sporadic cases) and papillary serous, clear cell or undifferentiated in histology, has a more aggressive clinical behavior and a less favorable prognosis [2].

According to recently published guidelines, systematic surgical staging represents the initial therapeutic approach in EC patients [3-6]. Treatment planning should be made by a multidisciplinary team (MDT) including: gynecological oncologist, radiation oncologist, medical oncologist, pathologist and radiologist [6]. During the MDT meeting, all available treatment options should be considered and the extent of surgical procedure and the type of postoperative adjuvant treatment should be carefully individualized according to disease stage, histologic subtype, fertility issues and patient general status [3-6].

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The systematic surgical staging in patients with EC includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and complete resection of any suspicious lesion [3-6]. Especially, in patients with cervical stroma involvement, a modified radical hysterectomy should be performed in order to obtain clear margins [3-6]. Furthermore, in EC patients with a high risk disease (tumor grade III, nonendometrioid histology), total omentectomy is a necessary part of the systematic surgical staging procedure [3-6]. Although peritoneal washings have no effect on FIGO staging, they should be obtained in all EC cases as positive result represents an adverse risk factor [3-6].

All these systematic surgical staging procedures should be performed by a Gynaecologist with appropriate training in Gynaecological Oncology, using either the open (laparotomy) or the minimally invasive (laparoscopy and robotic-assisted surgery) surgical approach [3-6]. Both surgical approaches can be used in EC patients with early stage disease, as they provide similar recurrence, overall survival and disease-free survival rates [4-6]. However, in high risk EC patients as well as in patients with advanced stage disease, laparotomy is the standard surgical approach allowing complete surgical staging and aggressive cytoreduction [3-6].

Pelvic and para-aortic lymphadenectomy represents an essential part of systematic surgical staging in EC patients, as this is the only way to diagnose accurately FIGO stage IIIC disease [3-6]. The systematic pelvic lymph node dissection includes: removal of the lymphatic tissue from the distal half of the common iliac vessels, the external iliac vessels (down to the deep circumflex iliac

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vein) and the obturator fossa (above to the obturator nerve) [3-6]. Likewise, the systematic para-aortic lymph node dissection includes: removal of the lymphatic tissue from the aorta and the inferior vena cava (up to the level of renal vessels or inferior mesenteric artery) [3-6].

Based on the SEPAL study findings, the systematic pelvic and para-aortic lymph node dissection should be routinely performed in intermediate and high risk EC patients (stage IB or more in type I EC and any stage in type II EC), as they offer survival benefits [7]. There is a direct correlation between the extent of the systematic pelvic and para-aortic lymphadenectomy and the risk for perioperative complications (vascular or nerve injury, lymphocyst, lymphoedema and cellulitis formation) [3, 8-10]. Especially, in elderly or obese patients with co-existing comorbidities (diabetes mellitus, coronary artery disease), there is a substantial increase in morbidity and perioperative complication rates, that should be carefully balanced with any survival advantage [3, 8-10].

According to the FIRES trial findings, sentinel lymph node mapping and dissection could be routinely performed in EC patients with early stage disease [11]. The main advantage of the sentinel lymph node technique, is the significant reduction of perioperative complications [3-6, 12]. Apart from identified sentinel lymph nodes, all enlarged or suspicious lymph nodes should also be removed based on the established surgical algorithm [12, 13]. In case of technique failure in one side, a side-specific systematic pelvic lymph node dissection should be performed [12]. All dissected sentinel lymph nodes should be evaluated with the ultra-staging approach [12].

In EC patients with early stage disease (stage I and II) and one or more adverse risk factors (age ≥60 years, depth of invasion >50%, tumor volume, lymphovascular space invasion, tumor grade III, nonendometrioid histology), postoperative adjuvant treatment (radiotherapy and/or systemic therapy) should be administered [3-6].

More specifically, in high-intermediate risk EC patients (age ≥60 years, depth of invasion >50%, lymphovascular space invasion) with early stage disease, postoperative adjuvant radiotherapy remains the treatment of choice based on findings of the GOG-99 and PORTEC-1 trials [3-6, 14, 15]. Adjuvant radiotherapy could be either vaginal brachytherapy and/or external pelvic radiotherapy and should be initiated no longer than 3 months after the systematic surgical staging [5]. Both radiotherapeutic approaches minimize the risk for local recurrences, but have no effect on overall and disease free survival (GOG-99, PORTEC-1 and PORTEC-2 trials) [14-16]. When comparing both of them, vaginal brachytherapy is more tolerated and associated with fewer side effects and better quality of life (PORTEC-2 trial) [16].

Moreover, in high risk EC patients (tumor grade III, nonendometrioid histology) with early stage disease, postoperative adjuvant radiotherapy could be possibly combined with postoperative adjuvant systemic therapy, based on the PORTEC-3 trial findings [17]. It seems that the combination of both therapeutic approaches in high risk EC patients with early stage disease, is associated with persistent sensory neurological symptoms and a minimal improvement in overall and disease free survival (GOG-249 and PORTEC-3 trial) [17, 18].

In EC patients with advanced stage disease (stage III and IV), postoperative adjuvant treatment (systemic therapy and/or radiotherapy) should also be administered [3-6].

More specifically, in EC patients with advanced stage disease, postoperative adjuvant systemic therapy represents the treatment of choice according to the GOG-122 trial findings [19]. Adjuvant multiagent systemic therapy (doxorubicin - cisplatin) significantly improves overall and disease free survival in EC patients with advanced stage disease, when compared with whole abdomen radiotherapy alone (GOG-122 trial) [19]. However, the administration of multiagent systemic therapy was associated with increased toxicity rates (GOG-122 trial) [19].

Moreover, in EC patients with advanced stage disease, postoperative adjuvant systemic therapy could be combined with adjuvant radiotherapy, based on the PORTEC-3 trial findings [17]. It seems that the combination of both therapeutic approaches in EC patients with stage III disease, is associated with significant improvement in overall and disease free survival, when compared with external radiotherapy alone (PORTEC-3 trial) [17]. Moreover, the combination of both therapeutic approaches in EC patients with stage III or IVA disease, does not provide any benefit regarding disease free survival, when compared with systemic therapy alone (GOG-258 trial) [20].

In conclusion, systematic surgical staging remains the initial therapeutic approach in EC patients [3-6]. In these cases, all available treatment options should be considered by a multidisciplinary team (MDT) and treatment planning should be carefully individualized based on disease stage, histologic subtype, fertility issues and patient performance status [3-6].

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