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Current Treatment Approach of Endometrial Cancer

Review Article

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Abstract

Systematic surgical staging is the primary treatment, for most patients with endometrial cancer and includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and complete resection of all disease. Especially in patients with type II endometrial cancer, systematic surgical staging includes additional omentectomy, appendectomy and biopsy of any suspected lesion. Although pelvic washings are no longer part of FIGO surgical staging system for endometrial cancer, they should be reported separately.

Especially in endometrial cancer patients with increased risk for recurrence or at advanced stage disease, it is necessary a more aggressive treatment approach with postoperative adjuvant radiotherapy and/or chemotherapy.

Postoperative adjuvant radiotherapy in endometrial cancer patients includes vaginal brachytherapy and external radiotherapy. Vaginal brachytherapy is the adjuvant treatment of choice for intermediate risk endometrial cancer patients. External pelvic radiotherapy is the adjuvant treatment of choice only in high risk endometrial cancer patients.

Postoperative adjuvant chemotherapy has very important role for endometrial cancer patients with advanced stage disease.

The combination of adjuvant chemotherapy and radiotherapy is promising in high risk endometrial cancer patients or in endometrial cancer patients at advanced stage disease.

Molecular targeted therapies have only modest effect in unselected endometrial cancer patients. Especially the role of ErbB-targeted therapies in selected EC patients, should be further investigated.

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Introduction

The most common malignancy of the female genital tract, is endometrial cancer (EC) [1]. It mainly occurs in postmenopausal women.[1-4] Overall, 2.64% of women will develop EC during their lifetime [1]. The most common symptom in patients with

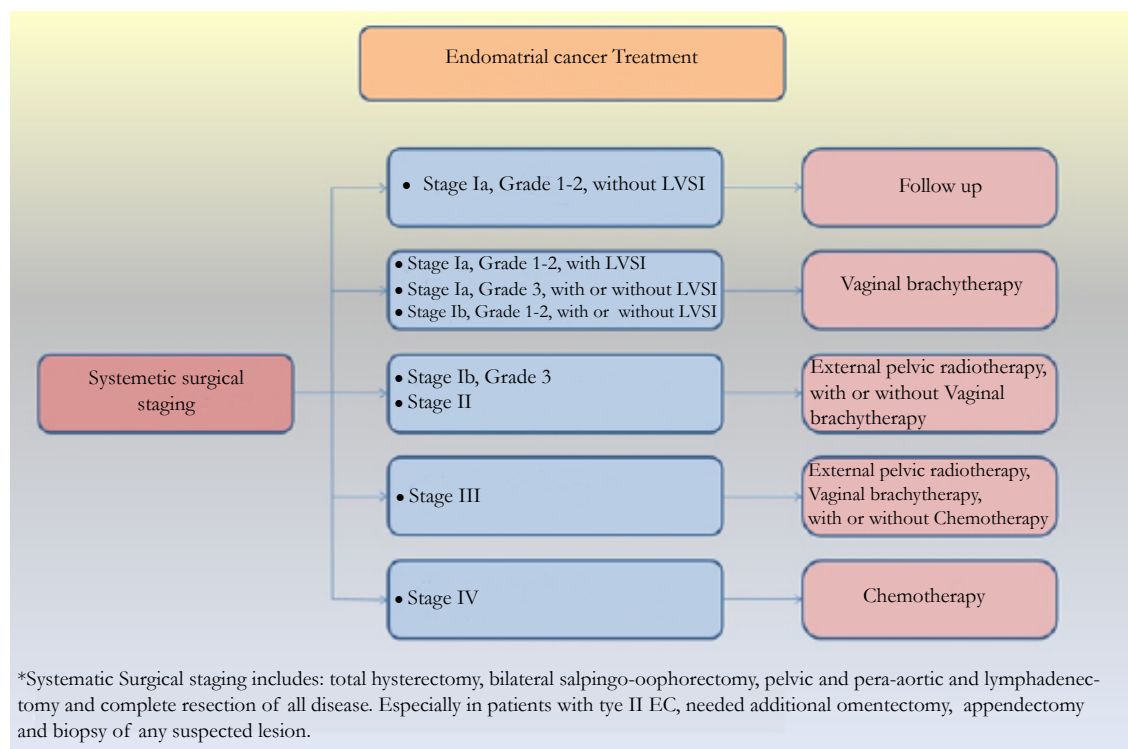
EC is abnormal uterine bleeding [2].

Based on clinical and pathological characteristics, sporadic EC classified into 2 types [5, 6]. Type I EC, constitutes the majority of sporadic EC cases (70-80%) [5, 6]. It is well differentiated, endometrioid in histology, has less aggressive clinical course and favorable prognosis [5-7]. Type II EC, constitutes the minority of sporadic EC cases (10-20%) [5, 6]. It is poorly differentiated, papillary serous or clear cell in histology, has aggressive clinical course and poor prognosis [5, 6, 8, 9].

Surgical Treatment

Systematic surgical staging is the primary treatment, for most patients with EC [2-4, 10-15] That therapeutic approach allows a clearer decision for the appropriate postoperative adjuvant therapy [Figure 1] [11].

In patients with EC, systematic surgical staging includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and complete resection of all disease [2, 11, 13, 14] Especially in patients with type II EC, systematic surgical staging includes additional omentectomy, appendectomy and biopsy of any suspected lesion [14, 16]. Although pelvic washings are no longer part of FIGO surgical staging system for EC, they should be reported separately [12].

Figure 1. Endometrial cancer treatment [2-4,11-13, 15, 30, 33, 40, 42, 44, 51, 54].

Appropriate surgical staging has diagnostic, prognostic and therapeutic advantages for women with EC [2-4, 11]. Moreover, it facilitates the implementation of targeted therapy maximizing the survival and minimizing the morbidity of overtreatment (radiation injury) and the effects of undertreatment (recurrent disease, increased mortality) [11].

Pelvic and para-aortic lymphadenectomy is very important for the surgical staging in patients with EC [3, 4, 10, 11, 13]. It identifies precisely the extent of the disease and affects the prognosis of EC patients [10, 14, 17]. Actually, it is the only way to diagnose EC patients with stage IIIc disease [11, 12, 18, 19]. Undoubtedly, it provides important informations for the need, type and extent of postoperative adjuvant treatment [10, 14, 17, 20].

Furthermore, pelvic and para-aortic lymphadenectomy has significant therapeutic advantages for patients with EC [21-23]. It is correlated with enhanced survival in patients with advanced stage type I EC and in all patients with type II EC [2, 21, 22, 24, 25]. However, it has no survival effect in patients with early stage type I EC [2, 13, 26, 27].

It appears that pelvic and para-aortic lymphadenectomy can be avoided safely in patients with early stage well differentiated type I EC [11, 26-29]. However pelvic and para-aortic lymphadenectomy should be performed in patients with advanced stage type I EC and in all patients with type II EC [3, 4, 24, 30, 31]. Also in any case of doubt, lymphadenectomy should be performed rather than avoided [3, 4, 30].

The extent of pelvic and para-aortic lymph node dissection (more than 14 lymph nodes) is an independent risk factor for postoperative complications [26, 29, 32]. Especially in elderly patients and in patients with various comorbidities (obesity, diabetes, coronary artery disease), intraoperative and postoperative morbidity must be carefully weighed against any survival advantage [11, 32-34].

In most EC patients, systematic surgical staging performed with laparotomy [14, 35, 36]. Especially in EC patients with early stage disease, systematic surgical staging can be performed with minimally invasive techniques (laparoscopy, robotic-assisted surgery) [2, 11, 13, 14, 35-38].

Minimally invasive surgery associated with smaller incisions, improved visualization, shorter hospital stay, less need for analgesics, quicker recovery and lower risk of complications (blood loss, wound infection, herniation, ileus) [11, 13, 14, 35-38]. Especially in overweight and elderly patients, minimally invasive surgery associated with significant advantages [11, 35-39]. Compared minimally invasive surgery and laparotomy, there are relatively small differences in recurrence rates [35, 36]. However, minimally invasive surgery and laparotomy associated with similar overall and disease-free survival [13, 14, 35, 36].

Adjuvant Treatment

Especially in EC patients with increased risk for recurrence or at advanced stage disease, it is necessary a more aggressive treatment approach with postoperative adjuvant radiotherapy and/or chemotherapy [Figure 1] [2, 10, 14, 15, 30].

Radiotherapy

Postoperative adjuvant radiotherapy in EC patients includes vaginal brachytherapy and external radiotherapy [Figure 1] [14, 40]

Vaginal brachytherapy in EC patients with early stage disease is well tolerated, reduces the risk of local recurrences but has no impact on overall survival [40-43]. Furthermore, it is associated with less side effects and better quality of life [40-43]. It is the adjuvant treatment of choice for intermediate risk EC patients (stage IA grade 3 endometrioid type EC, stage IB grade 1-2 endometrioid

Especially for intermediate risk EC patients, vaginal brachytherapy is equivalent to external pelvic radiotherapy in achieving local control of disease [14, 40, 41, 44, 45]. Moreover vaginal brachytherapy in those EC patients, have significant advantages in the quality of life [14, 40, 41, 44, 45].

External pelvic radiotherapy in EC patients with early stage disease, reduces the risk of local recurrences but has no impact on overall survival [11, 40-42, 47, 48]. Nevertheless, it is associated with significant morbidity and reduction in quality of life [41, 47]. It is the adjuvant treatment of choice only in high risk EC patients (stage IB grade 3 endometrioid type EC, stage I non-endometrioid type EC) [Figure 1] [14, 43-45].

In EC patients with advanced stage disease, although external pelvic radiotherapy reduces the risk of local recurrences it has no impact on overall survival [11, 40, 44].

Whole abdomen radiotherapy in EC patients with advanced stage disease, has tolerable toxicity and may improve survival [49]. Nevertheless, it can be used only in patients with completely resected disease [49].

Chemotherapy

Postoperative adjuvant chemotherapy has very important role for EC patients with advanced stage disease [Figure 1] [2, 10, 14, 40, 50, 51]. The most active chemotherapeutic agents for EC patients with advanced stage disease, are: taxanes, anthracyclines and platinum compounds [50, 52].

Adjuvant chemotherapy has only modest effect in progression free survival and overall survival, although it achieves high response rates [50]. Furthermore in EC patients with advanced stage disease, adjuvant chemotherapy is more effective than whole abdomen radiotherapy [30, 53].

Chemotherapy and Radiotherapy

The combination of adjuvant chemotherapy and radiotherapy is promising in high risk EC patients or in EC patients at advanced stage disease [Figure 1] [40, 50, 54]. Especially in EC patients with completely resected disease, the combination of adjuvant chemotherapy and radiotherapy reduce the risk of relapse or death and increase overall survival [14, 40, 55]. Furthermore, the combination of adjuvant chemotherapy and radiotherapy is more effective than adjuvant radiotherapy alone [40, 50, 55].

Molecular Targeted Therapies

In recent years, molecular targeted therapies have only modest effect in unselected EC patients [50]. They usually target the signaling pathways of EGFR, VEGFR and PI3K/PTEN/AKT/mTOR [56-58].

Especially the role of ErbB-targeted therapies in selected EC patients, should be further investigated in clinical trials [15, 58-68]. Perhaps ErbB-targeted therapies may be used as adjuvant treatment in type II EC patients with EGFR and ErbB-2 overexpression [15, 59, 65, 67-69]. Moreover further studies into the molecu-

lar pathways of EC, may increase our knowledge and lead to the discovery of new generation molecules with greater therapeutic efficacy [63].

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Special Issue on

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