Editorial

Endometrial Cancer: Current Treatment Strategies

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Endometrial cancer (EC) is the most common malignancy of the female genital tract. [1] It occurs primarily in postmenopausal women [1-5]. Overall, 2.64% of women develop EC during their lifetime [1]. In patients with EC, the most common presenting symptom is abnormal uterine bleeding [2].

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

Systematic surgical staging is the baseline therapy, for most patients with EC [2-4, 11-15]. That therapeutic approach allows a more clear decision for stage related postoperative adjuvant therapy [12].

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, 12, 14, 15]. Especially in patients with type II EC, systematic surgical staging requires additional omentectomy, appendectomy and biopsy of any suspected lesion [15, 16]. Pelvic washings are no longer part of FIGO surgical staging system for EC, but may be reported separately [13].

Appropriate surgical staging provides diagnostic, prognostic and therapeutic benefits for women with EC [2-4, 12]. It facilitates targeted therapy that maximize survival and minimize the morbidity of over treatment (radiation injury) and the effects of under treatment (recurrent disease, increased mortality) [12].

Pelvic and para-aortic lymphadenectomy is essential for surgical staging in patients with EC [3 4 11 12 14]. It defines accurately the extent of disease and determines the prognosis of EC patients [11 15 17]. It is the only way to identify EC patients with stage IIIc disease [12, 13, 18, 19]. Also, it provides a rationale for the need, type and extent of postoperative adjuvant treatment [11, 15, 17, 20].

Moreover, pelvic and para-aortic lymphadenectomy have therapeutic benefits for patients with EC [21-23]. It is associated with improved survival in all patients with type II EC and in patients with advanced stage type I EC [2 21 22, 24, 25]. However it has no effect on survival in patients with early stage type I EC [2, 14, 26, 27].

It seems that pelvic and para-aortic lymphadenectomy can be safely omitted in patients with early stage well differentiated type I EC [12, 26-29]. However pelvic and para-aortic lymphadenectomy should be performed in all patients with type II EC and in patients with advanced stage type I EC [3, 4, 24, 30, 31]. Also in any case of doubt, lymphadenectomy should be performed rather than abandoned [3, 4, 30].

The extension 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 relevant comorbidities (obesity, diabetes, coronary artery disease), morbidity must be carefully weighed against any survival advantage [12, 32-34].

In most EC patients, systematic surgical staging performed with laparotomy [15, 35, 36]. However in EC patients with early stage disease, systematic surgical staging can be performed with minimally invasive techniques (laparoscopy, robotic-assisted surgery) [2, 12, 14, 15, 35-38]. Minimally invasive surgery associated with smaller incisions, improved

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visualization, shorter hospital stay, less need for analgesics, quicker recovery and lower risk of complications (blood loss, wound infection, herniation, ileus) [12, 14, 15, 35-38]. Moreover, it offers many advantages especially in overweight and elderly patients [12, 35-39]. Compared with laparotomy, minimally invasive surgery associated with similar overall and disease-free survival [14, 15, 35, 36]. However, there are relatively small differences in recurrence rates [35, 36].

Especially in EC patients with increased risk for recurrence or at advanced stage disease, required a more aggressive management with postoperative adjuvant radiotherapy and/or chemotherapy [2, 11, 15, 30].

Postoperative adjuvant radiotherapy in EC patients includes vaginal brachytherapy and external radiotherapy [15, 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]. Moreover, 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 type EC) [15, 40-42, 44-46].

Especially for intermediate risk EC patients, vaginal brachytherapy is equivalent to external pelvic radiotherapy in achieving local control of disease [15, 40, 41, 44, 45]. Moreover vaginal brachytherapy in those EC patients, have significant advantages in the quality of life [15, 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 [12, 40-42, 47, 48]. However, it is associated with significant morbidity and reduction in quality of life [41, 47]. It is used only in high-risk EC patients (stage IB grade 3 endometrioid type EC, stage I non-endometrioid type EC) [15, 43-45].

External pelvic radiotherapy in EC patients with advanced stage disease, reduces the risk of local recurrences but has no impact on overall survival [12, 40, 44].

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

Postoperative adjuvant chemotherapy is the mainstay of treatment for EC patients with advanced stage disease [2, 11, 15, 40, 50, 51]. In those EC patients, the most active chemotherapeutic agents are: taxanes, anthracyclines and platinum compounds [50 52]. Although adjuvant chemotherapy achieve high response rates, it has only modest effect in progression free survival and overall survival [50]. Moreover adjuvant chemotherapy in EC patients with advanced stage disease, is more effective than whole abdomen radiotherapy [30, 53].

The combination of adjuvant chemotherapy and radiotherapy is promising in high-risk EC patients or at advanced stage disease [40, 50, 54]. In those EC patients with completely resected disease, the combination of adjuvant chemotherapy and radiotherapy reduce the risk of relapse or death and increase overall survival [15, 40, 55]. Moreover, the combination of adjuvant chemotherapy and radiotherapy is more effective than adjuvant radiotherapy alone [40, 50, 55].

Recent years, molecular targeted therapies have still shown modest effect in unselected EC patients [50]. They usually target the inhibition of EGFR, VEGFR and PI3K/PTEN/AKT/mTOR signal pathways [56].

Especially the role of ErbB-targeted therapies in EC, should be further investigated in clinical trials [57-64]. Perhaps they are active as adjuvant therapy in well-defined subgroups of type II EC patients with EGFR and ErbB-2 over expression [5, 57, 63, 65]. Moreover additional studies into the molecular pathways of EC development and progression, will increase our knowledge and lead to the discovery of new generation molecules with higher therapeutic efficacy [61].

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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