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Present and future in endometrial cancer treatment

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In the developed world, endometrial cancer (EC) is the most frequent female genital tract malignancy.[1–5] The lifetime risk of developing EC is 2.64%.[1] It most commonly occurs in postmenopausal women.[1–5] Moreover based on its clinical and pathological features, sporadic EC classified into 2 types (type I EC and type II EC).[6,7]

According to ACOG, FIGO, SGO and ESMO recommendations, systematic surgical staging is the primary treatment for EC patients.[3–5,8–12] Especially in patients with type I EC (endometrioid), systematic surgical staging includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and complete resection of all disease.[2–5,8–13] However in patients with type II EC (poorly differentiated, papillary serous, clear cell), systematic surgical staging includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and additional omentectomy, appendectomy and biopsy of any suspected lesion.[3–5,10,11,14] Positive pelvic washings should be reported separately, although they do not affect FIGO staging for EC.[9]

Laparotomy is the preferable surgical technique for systematic surgical staging in most EC patients.[3–5,10,11,15,16] However in EC patients with early stage disease, we can also use minimally invasive techniques (laparoscopy, robotic-assisted surgery) for the same purpose.[2–5,8,10–12,15–18]

It is widely accepted that minimally invasive techniques have many significant advantages (smaller incisions, improved visualization, shorter hospital stay, less need for analgesics, quicker recovery and lower risk of postoperative complications).[3–5,8,10–12,15–19] Those advantages are very important, especially in overweight and elderly patients.[3–5,8,10–12,15–19]

The various surgical techniques (laparotomy, minimally invasive techniques) that applied in EC patients, have relatively small differences in recurrence rates.[15,16] Moreover, those surgical techniques (laparotomy, minimally invasive techniques) associated with similar overall and disease-free survival rates.[10,12,15,16]

It should be mentioned that pelvic and para-aortic lymphadenectomy, are absolutely necessary in EC patients for the diagnosis of stage IIIc disease.[3–5,8,9,11–13,20,21] Moreover the application of pelvic and para-aortic lymphadenectomy in patients with advanced stage type I EC and in all patients with type II EC, associated with improved survival.[2–5,11,22–26] However the application of pelvic and para-aortic lymphadenectomy in patients with early stage type I EC, do not improve survival.[2–5,11,12,27,28]

Moreover the extent of pelvic and para-aortic lymphadenectomy (>14 lymph nodes), increases significantly the risk for postoperative complications.[3–5,11,27,29,30] Especially in elderly patients and in patients with relative comorbidities (obesity, diabetes, coronary artery disease), pelvic and para-aortic lymphadenectomy increases significantly the intraoperative and postoperative morbidity.[3–5,8,11,29,31,32] In any case, the intraoperative and postoperative morbidity must be carefully weighed against any survival advantage.[3–5,11,29,31,32]

It is obvious that the application of systematic surgical staging in EC patients, has diagnostic, prognostic and therapeutic benefits.[2–5,8,11] Moreover, systematic surgical staging allows a more clear decision for the selection of the appropriate postoperative adjuvant treatment.[3–5,8,11] Additionally, the application of the appropriate postoperative adjuvant treatment maximize survival and minimize the morbidity of overtreatment (radiation injury) and the effects of undertreatment (recurrent disease, increased mortality).[3–5,8,11]

However according to ACOG, SGO and ESMO recommendations, the application of postoperative adjuvant treatment (radiotherapy and/or chemotherapy) is absolutely necessary, particularly in EC patients with increased risk for recurrence or at advanced stage disease.[2–5,8,10,13,33,34] More specifically, the application of postoperative adjuvant radiotherapy in EC patients includes vaginal brachytherapy and external radiotherapy.[3–5,10,11,34]

Vaginal brachytherapy is the adjuvant treatment of choice particularly in intermediate risk EC patients (stage IA grade 3 endometrioid type EC, stage IB grade 1-2 endometrioid type EC).[3–5,10,11,34–39] It is well tolerated, reduces the risk for local recurrences but has no impact on overall survival.[34,35,38,40] Moreover, the application of vaginal brachytherapy associated with less side effects and better quality of life.[10,34–38,40] Additionally in intermediate risk EC patients, the application of vaginal brachytherapy is equivalent to the application of external pelvic radiotherapy in achieving local control of disease.[3–5,10,11,34–37]

External pelvic radiotherapy is the adjuvant treatment of choice particularly in high risk EC patients (stage IB grade 3 endometrioid type EC, stage I non-endometrioid type EC).[3–5,10,11,36,37,40] Although it reduces the risk for local recurrences, it has no impact on overall survival.[3–5,8,34–36,38,41,42] However, the application of external pelvic radiotherapy associated with significant morbidity and reduction in quality of life.[3–5,11,35,41]

Whole abdomen radiotherapy can be used in EC patients with advanced stage disease.[43] However, it can be used only in patients with completely resected disease.[43] Moreover, the application of whole abdomen radiotherapy has tolerable toxicity and may improve overall survival.[3–5,11,43]

Postoperative adjuvant chemotherapy is the adjuvant treatment of choice particularly in EC patients with advanced stage disease.[2–5,10,11,13,34,44,45] The most active chemotherapeutic agents

for those EC patients, are: taxanes, anthracyclines and platinum compounds.[44,46] Although the application of adjuvant chemotherapy achieves high response rates, it has only modest effect in progression free survival and overall survival.[3–5,11,44] Moreover, the application of adjuvant chemotherapy is more effective than the application of whole abdomen radiotherapy.[3–5,11,33,47]

Combined application of adjuvant chemotherapy and radiotherapy is a promising adjuvant treatment particularly in high risk EC patients and in EC patients at advanced stage disease.[3–5,11,34,44,48] Especially in EC patients with completely resected disease, the combined application of adjuvant chemotherapy and radiotherapy significantly reduce the risk of relapse or death and increase overall survival.[3–5,10,11,34,49] Moreover, the combined application of adjuvant chemotherapy and radiotherapy is more effective than the application of adjuvant radiotherapy alone.[3–5,11,34,44,49]

Recent years, molecular targeted therapies have increasing popularity.[3–5,11] However, they have only modest effect in unselected EC patients.[3–5,11,44,50–53] Moreover the application of molecular targeted therapies, usually target the signaling pathways of EGFR, VEGFR and PI3K/PTEN/AKT/Mtor.[54–56] More specifically, ErbB-targeted therapies can be used as adjuvant treatment especially in type II EC patients with EGFR and ErbB-2 overexpression.[3–5,11,50–53,56–63] However, additional studies into the molecular pathways of EC are necessary.[3–5,11,50–52,62,63]

It is obvious that the present and future in endometrial cancer treatment is extremely challenging, especially regarding the application of postoperative adjuvant treatment in EC patients with increased risk for recurrence or at advanced stage disease.

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Conflicts of interest

The authors declare there is no conflict of interests.

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