Journal of
Gynecology and Women's Health
ISSN 2474-7602

Juniper Publishers
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Editorial
Volume 1 Issue 3 - September 2016

J Gynecol Women's Health

Standard and Novel Therapies in Endometrial Cancer

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Submission: September 13, 2016; **Published:** September 16, 2016

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Editorial

In developed countries, endometrial cancer (EC) represents the most common malignancy of the female genital tract [1-8]. Especially in the United States, the average life time risk for EC is about 2.64%. EC usually affects postmenopausal women and the most common presenting symptom is abnormal uterine bleeding [1-9]. Based on the clinical and pathological features, sporadic EC classified into 2 different types (type I EC and type II EC). Type I EC, represents the majority of sporadic EC cases (70-80%), is usually well differentiated and endometrioid in histology Type II EC, represents the minority of sporadic EC cases (10-20%), is poorly differentiated and usually papillary serous or clear cell in histology. The classification of sporadic EC plays an essential role for the entire management of the disease [10,11].

Recent years, many international scientific societies (ACOG, FIGO, SGO and ESMO) have recommended the systematic surgical staging as the initial treatment approach in patients with malignancies of the female genital tract. This is mainly because systematic surgical staging offers a lot of diagnostic, prognostic and therapeutic benefits in those patients [2-4,6,12-15]. Especially in patients with type I EC, the systematic surgical staging includes: total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and complete resection of any suspicious lesion [2-8,12-16]. In contrast, the systematic surgical staging in patients with type II EC, requires additional total omentectomy and appendectomy [2-8,12-17].

Pelvic washings are also necessary for both types of EC, although they do not affect FIGO staging [13]. The systematic surgical staging in EC patients can be performed either with the standard (laparotomy) or the minimally invasive (laparoscopy and robotic-assisted surgery) approach. Laparotomy is the preferable surgical approach for the systematic surgical staging especially in EC patients with advanced stage disease. Minimally invasive approaches are mainly applied in EC patients with early stage disease [2-8,12,14,15,18-21]. Both surgical approaches when applied in EC patients, achieve similar recurrence, overall survival and disease-free survival rates [14,15,20,21]. However, minimally invasive techniques offer great advantages mainly in overweight and elderly EC patients (smaller incisions, better visualization, shorter hospital stay, less postoperative pain, quick recovery and low risk for postoperative complications) [2-8,12,14,15,18-22].

Moreover, minimally invasive techniques are significantly more difficult and time consuming and require special surgical skills. This is the reason why, most surgeons prefer them only in EC patients with early stage disease [2-8,12,14,15,18-22]. It is interesting to note, that pelvic and para-aortic lymphadenectomy plays an essential role in the systematic surgical staging of EC patients [2-4,6-8,23]. This is the only way to diagnose correctly, EC patients at stage IIIc [2-4,6-8,12,13,15,16,23,24]. Moreover, pelvic and para-aortic lymphadenectomy offers survival benefits and improves overall survival in patients with advanced stage type I EC and in all patients with type II EC [2-8,25-29]. In sharp contrast, pelvic and para-aortic lymphadenectomy does not offer survival benefits in patients with early stage type I EC [2-8,15,30,31].

Additionally, there is an obvious increase in morbidity and postoperative complications rates, in cases with extended pelvic and para-aortic lymph node dissection (more than 14 lymph nodes) [2-4,6-8,30,32,33]. This is the reason why, every surgeon should carefully weigh the increased morbidity and the risk for postoperative complications with any survival advantage, especially in elderly patients and in patients with comorbidities (obesity, diabetes mellitus and coronary artery disease) [2-4,6-8,12,32,34,35]. On the other hand, according to the recent recommendations of the international scientific societies (ACOG, FIGO, SGO and ESMO), postoperative adjuvant treatment (radiotherapy and/or chemotherapy) plays an equally important role in EC patients with increased risk of recurrence or at advanced disease stage [2-8,12,14,16,36,37].

Based on the recommendations above, vaginal brachytherapy represents the adjuvant treatment of choice in intermediate risk EC patients (stage IA grade 3 endometrioid type EC, stage IB grade 1-2 endometrioid type EC) [2-4,6-8,14,37-42]. According to the PORTEC Study Group (PORTEC I and PORTEC II trials), vaginal brachytherapy is well tolerated and associated with less side effects and better quality of life [2-4,6-8,14,37-41,43]. In addition,

vaginal brachytherapy minimizes the risk for local recurrences, although it does not affect overall survival [2-4,6-8,37,38,41-43]. Furthermore, vaginal brachytherapy and external pelvic radiotherapy play are equivalent in achieving local control of the disease in intermediate risk EC patients [2-4,6-8,14,37-40].

Likewise, external pelvic radiotherapy represents the adjuvant treatment of choice in high risk EC patients (stage IB grade 3 endometrioid type EC, stage I non-endometrioid type EC) [2-4,6-8,14,39,40,43]. According to the PORTEC Study Group (PORTEC II trial), external pelvic radiotherapy is not well tolerated and associated with more side effects, significant morbidity and impairment in quality of life [2-4,6-8,38,44]. Additionally, external pelvic radiotherapy minimizes the risk for local recurrences, although it does not affect overall survival [2-4,6-8,12,37-39,41,44,45]. In contrast, whole abdomen radiotherapy represents an alternative treatment approach in EC patients with advanced stage disease. It has tolerable toxicity and may improve overall survival [2-4,6-8,46]. However, only patients with completely resected disease are eligible for whole abdomen radiotherapy [46]. Postoperative adjuvant chemotherapy represents the adjuvant treatment of choice in EC patients with advanced stage disease [2-8,14,16,37,47,48]. The most common chemotherapeutic regimens in EC patients, are: taxanes, anthracyclines and platinum compounds [47,49]. The administration of postoperative adjuvant chemotherapy in EC patients achieves high response rates, but it has only modest effect in progression free survival and overall survival rates [2-4,6-8,47]. Compared with whole abdomen radiotherapy, adjuvant chemotherapy is more effective and offers more survival benefits in EC patients with advanced stage disease [2-4,6-8,36,50].

The combined postoperative application of adjuvant radiotherapy and adjuvant chemotherapy represents an alternative treatment choice, especially in high risk EC patients and in EC patients at advanced stage disease [2-4,6-8,37,47,51]. The administration of postoperative adjuvant radiotherapy and adjuvant chemotherapy in EC patients with systematic surgical staging reduces the risk of relapse or death and increases overall survival. Compared with the isolated postoperative adjuvant radiotherapy, the combined postoperative adjuvant radiotherapy and adjuvant chemotherapy is more effective in high risk EC patients and in EC patients at advanced stage disease [2-4,6-8,14,37,47,52]. According to the PORTEC Study Group (PORTEC III trial) after completion of the combined adjuvant treatment, approximately 25% of patients have persistent sensory neurological symptoms [53].

During the last decade, molecular therapies targeting essential signaling pathways (EGFR, VEGFR and PI3K/PTEN/AKT/mTOR) have become very popular in the treatment of various types of cancer [2-4,6-8,54-66]. However, the postoperative application of those therapies achieves only modest response rates, unless if they are associated with chemotherapy or radiotherapy [2-4,6-8,47,57-69]. Moreover, those therapies have not studied well in EC and they have only modest effect in unselected EC patients [2-4,6-8,47,57-66]. Patients with type II EC, represent an eligible target for the ErbB-targeted therapies [70]. Perhaps, ErbB-targeted therapies can be used as an adjuvant treatment in well-defined subgroups of EC patients (type II EC) with EGFR and ErbB-2 over expression. In this light, their efficacy should be further evaluated with prospective clinical trials in well-defined subgroups of EC patients [2-4,6-8,56-66,70-74].

In conclusion, the systematic surgical staging remains the standard treatment approach in EC patients and offers a lot of diagnostic, prognostic and therapeutic benefits. Additionally, systematic surgical staging affects the decision for the postoperative adjuvant treatment, in order to maximize survival and minimize the morbidity of over-treatment and the effects of under-treatment [2-8,12]. Regarding ErbB-targeted therapies, their efficacy should be further evaluated with prospective clinical trials [2-4,6-8,56-66,70-74].

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How to cite this article: Androutsopoulos G, Decavalas G. Standard and Novel Therapies in Endometrial Cancer. J Gynecol Women's Health. 2016; 1(3): 555564. DOI: 10.19080/JGWH.2016.01.555564

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How to cite this article: Androutsopoulos G, Decavalas G. Standard and Novel Therapies in Endometrial Cancer. J Gynecol Women's Health. 2016; 1(3): 555564. DOI: 10.19080/JGWH.2016.01.555564

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How to cite this article: Androutsopoulos G, Decavalas G. Standard and Novel Therapies in Endometrial Cancer. J Gynecol Women's Health. 2016; 1(3): 555564. DOI: 10.19080/JGWH.2016.01.555564