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Review

Clinical characteristics and current therapeutic approach of patients with synchronous primary endometrial and ovarian cancers

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Abstract

Synchronous primary endometrial and ovarian cancers are relatively uncommon in general population. Although their pathogenesis still remains unclear, embryologic, hormonal, genetic or other phenomena may be responsible for the development of synchronous primary endometrial and ovarian cancers. The most common symptoms and signs in those patients are: abnormal uterine bleeding, abdominal/pelvic pain and abdominal/pelvic mass. For most patients with synchronous primary endometrial and ovarian cancers, systematic surgical staging is the baseline therapy and includes total abdominal hysterectomy with bilateral salpingo - oophorectomy, total omentectomy, appendectomy, pelvic and para - aortic lymphadenectomy, complete resection of all disease, biopsy of any suspected lesion and pelvic washings. Moreover, that therapeutic approach allows a more clear decision for stage related postoperative adjuvant therapy. The role of postoperative adjuvant treatment in patients with synchronous primary endometrial and ovarian cancers, remains controversial. In most cases, postoperative adjuvant treatment should be individualized according to the risk of recurrence of each primary cancer. Particularly in patients with increased risk for recurrence or at advanced stage disease, postoperative adjuvant treatment customized to both cancers is required. Patients with synchronous primary endometrial and ovarian cancers have better overall survival than patients with single primary ovarian or endometrial cancer. Perhaps, favorable prognosis is associated with the detection of patients at early stage and low grade disease. Moreover, the clinical efficacy of the postoperative adjuvant treatment should be further investigated.

Key words: synchronous primary cancers; clinical characteristics; treatment

Synchronous primary cancers are relatively uncommon in general population[1-3]. Among women with gynecologic malignancies, only 0.5 - 1.7% have synchronous primary cancers of the female genital tract. The most common cancer combination in those patients, is synchronous primary en-

dometrial and ovarian cancers[4-9].

Epidemiology

There are distinct clinical characteristics in patients with synchronous primary endometrial and ovarian cancers including young age, obesity, premenopausal status and nulliparity[10]. The median age at diagnosis of synchronous primary endometrial and ovarian cancers is 50 years[4,9-15]. Usually, those patients are 10 - 20 years younger than patients with single endometrial or ovarian cancer[5,12,13,15,16].

Pathogenesis

Despite proposed theories, the pathogenesis of synchronous primary endometrial and ovarian cancers still remains unclear[2,3,7,17]. An attractive explanation of the development of synchronous primary cancers in the female genital tract is the theory of the secondary Müllerian system[6,7,17-19]. According to this theory, the common embryologic origin of the epithelia in the upper female genital tract, explains adequately their synchronous response to a carcinogenic stimulus (hormone, radiation, other)[2,6,17,18].

Possibly, common hormone receptors (estrogen receptors) in the upper female genital tract, are also responsible for the development of synchronous primary cancers[6,7,19]. Moreover, patients with synchronous primary endometrial and ovarian cancers, may have a more fragile genome and prior genetic damage may predispose them to the development of synchronous primary cancers[17,20-24]. Especially patients with Lynch syndrome, have an obvious predisposition to the development of multiple synchronous primary cancers (colon, endometrium, ovary, stomach, small bowel, ureter and renal pelvis)[25].

It is evident that embryologic, hormonal, genetic or other phenomena may be responsible for the development of synchronous primary endometrial and ovarian cancers[6,7,17-20,22,25].

Symptoms and signs

Patients with synchronous primary endometrial and ovarian cancers, have the following symptoms and signs: abnormal uterine bleeding (46%), abdominal/pelvic pain (17%) and abdominal/pelvic mass (13%)[1-3, 10, 12, 14, 15, 17, 26].

Pathology

Synchronous primary endometrial and ovarian cancers may have similar or different histologic appearance[7,11,16]. The distinction between synchronous primary and metastatic cancers is relatively easy, when they have different histologic types. However, the distinction is relatively difficult, when they have the same histologic type. In clinical practise, we use well described empirical criteria for the proper diagnosis of synchronous primary endometrial and ovarian cancers[27,28].

Treatment

Systematic surgical staging is the baseline therapy, for most patients with synchronous primary endometrial and ovarian cancers[1,2,4,5,7,11-14,29-31]. That therapeutic approach allows a more clear decision for stage related postoperative adjuvant therapy[1,2,30-33].

In patients with synchronous primary endometrial and ovarian cancers, systematic surgical staging includes total abdominal hysterectomy with bilateral salpingo - oophorectomy, total omentectomy, appendectomy, pelvic and para - aortic lymphadenectomy, complete resection of all disease, biopsy of any suspected lesion and pelvic washings[1,3,5,7,11-13,29-31,34,45].

Appropriate surgical staging provides diagnostic, prognostic and therapeutic benefits for women with synchronous primary endometrial and ovarian cancers. It facilitates targeted therapy that maximize survival and minimize the morbidity of overtreatment (radiation injury, chemotherapy toxicity) and the effects of undertreatment (recurrent disease, increased mortality)[1-3,32].

The role of pelvic and para - aortic lymphadenectomy is crucial for patients with synchronous primary endometrial and ovarian cancers. It defines precisely the extent of disease and the prognosis of patients. Moreover, pelvic and para - aortic lym-

phadenectomy is very important to identify patients with stage III disease[1-3,34,35].

An independent risk factor for postoperative complications, is the extent of pelvic and para - aortic lymph node dissection (more than 14 lymph nodes)[1-3,30,31,33,36-38]. Moreover, in elderly patients as well as in patients with relevant comorbidities (obesity, diabetes, coronary artery disease), morbidity should be carefully weighed against any survival advantage[1-3,32,39,40].

The role of postoperative adjuvant treatment in patients with synchronous primary endometrial and ovarian cancers, remains controversial[11,14,41]. In most cases with synchronous primary endometrial and ovarian cancers, postoperative adjuvant treatment should be individualized according to the risk of recurrence of each primary cancer[2,3,41,42]. Moreover, the postoperative adjuvant treatment of one primary cancer should not affect the postoperative adjuvant treatment of the other primary cancer[2,3,43].

Particularly in patients with increased risk for recurrence or at advanced stage disease, postoperative adjuvant treatment customized to both cancers is required[1-4,7,12-14,16,26,29-31,41,43-45]. More specifically in those patients, postoperative adjuvant treatment includes radiotherapy and/or chemotherapy[1-3,12,16,41]. Postoperative adjuvant radiotherapy includes: external pelvic radiotherapy and/or brachytherapy[1-3,30,31,33].

Vaginal brachytherapy is the adjuvant treatment of choice for intermediate risk endometrial cancer (EC) patients (stage IA grade 3 endometrioid type EC, stage IB grade 1 - 2 endometrioid type EC)[46-52]. It is well tolerated, reduces the risk of local recurrences but has no impact on overall survival. Moreover, it is associated with less side effects and better quality of life. Especially for intermediate risk EC patients, vaginal brachytherapy is equivalent to external pelvic radiotherapy in achieving local control of disease[46-51,53].

External pelvic radiotherapy is used only in high risk EC patients (stage IB grade 3 endometrioid type EC, stage I non - endometrioid type EC)[47-50,53]. It reduces the risk of local recurrences but has no impact on overall survival[32,46,48,51,54,55]. Moreover, it is associated with significant morbidity and reduction in quality of life[46,54].

Postoperative adjuvant chemotherapy is the appropriate treatment for patients with advanced stage disease[1-3,42]. The most active chemotherapeutic agents for patients with synchronous primary endometrial and ovarian cancers, are taxanes, anthracyclines and platinum compounds[12,14].

The clinical efficacy of the postoperative adjuvant treatment should be further investigated[41].

Prognosis

The most important prognostic factors for patients with synchronous primary endometrial and ovarian cancers include age, stage of ovarian cancer, grade of endometrial cancer and adjuvant treatment[45,56-57].

Patients with synchronous primary endometrial and ovarian cancers have 5 - year overall survival 85.9% and 10 - year overall survival 80.3%[11]. It is obvious that patients with synchronous primary endometrial and ovarian cancers have better overall survival than patients with single primary ovarian or endometrial cancer[1-3,10,41,43,45,58]. Moreover, patients with synchronous primary endometrial and ovarian cancers of endometrioid type have better overall survival than patients with non - endometrioid or mixed histologic types[1-3,10,41,45].

The better overall survival of those patients could be associated with the detection of patients at early stage and low grade disease[1-4,7,11,21-23,26,29,58,59].

Conflict of interest

All authors declare no conflict of interest.

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