

The management of clinically early ovarian cancer patients who have not undergone staging surgery

Evreleme ameliyatı geçirmemiş klinik olarak erken over kanseri hastalarının yönetimi

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Abstract

Four-thirds of patients with epithelial ovarian cancer are diagnosed at an advanced stage, and the main choice of treatment is primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy, or interval surgery after neoadjuvant chemotherapy in patients who are not eligible for optimal cytoreductive surgery. In patients with disease clinically confined to the ovary, The International Federation of Gynecology and Obstetrics (FIGO) recommends comprehensive staging to detect the real stage of the disease, but some these patients do not undergo staging during operation. Retrospective studies in the literature report that re-operation, adjuvant chemotherapy without re-operation or observation are some of the management options during the postoperative period for patients with clinically early stage disease. In this article, the management of these patients was reviewed in light of the current literature.

Keywords: Staging surgery, Chemotherapy, Ovarian carcinoma, Observation, Incomplete surgery

Öz

Epitelyal over kanseri olan hastaların dörtte üçüne ileri evrede iken tanı konur ve bu hastaların ana tedavisi primer sitoredüktif cerrahi, ardından adjuvan platin bazlı kemoterapi veya neoadjuvan kemoterapi sonrası sitoredüktif cerrahidir. Klinik olarak overde sınırlı hastalığı olan kadınlarında, Uluslararası Kadın Hastalıkları ve Doğum Federasyonu (FIGO) hastalığın gerçek evresinin tespiti için kapsamlı evreleme cerrahisi yapılmasını önermektedir, ancak bu hastalardan bazıları operasyon sırasında evreleme ameliyatı geçirmemiş olabilir. Literatürdeki retrospektif çalışmalarla göre, klinik olarak erken evre hastalığı olan bu hastalar için tekrar ameliyat, tekrar ameliyat olmadan adjuvan kemoterapi veya gözlem tedavi seçenekleri olarak uygulanmaktadır. Bu yazında, cerrahi evrelemesi yapılmamış bu hastaların yönetimi güncel literatür ışığında gözden geçirilmiştir.

Anahtar kelimeler: Cerrahi evreleme, Kemoterapi, Over kanseri, Gözlem, Tamamlanmamış cerrahi

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Conflict of Interest: No conflict of interest was declared by the authors.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.



Financial Disclosure: The authors declared that this study has received no financial support.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.



Published: 8/23/2019

Yayın Tarihi: 23.08.2019

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How to cite / Atf için: Kaban A, Ferlengen AG, Kaban I. The management of clinically early ovarian cancer patients who have not undergone staging surgery. J Surg Med. 2019;3(8):605-608.

Introduction

Ovarian cancer is the most lethal gynecological cancer worldwide [1]. The life-time risk of getting ovarian cancer is 1/70 [2]. According to GLOBOCAN data, disease-related death rates are 50% in cervical cancer, 25% in endometrium cancer and 67% in ovarian cancer [1]. At the time of diagnosis, 60-75% of the patients have advanced disease (FIGO III-IV) [3,4]. Histologically, more than 90% of ovarian carcinomas are epithelial type (EOC) and 70% of them are high grade tumors [5-9].

The standard treatment of patients with EOC is primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy. The goal of surgery is to achieve maximum (complete) cytoreduction. Many studies have shown that survival is directly associated with the rate of complete cytoreduction [10-13]. Neoadjuvant chemotherapy followed by interval surgery is considered an alternative option in patients who are not suitable for optimal surgery [13,14].

Patients with epithelial ovarian cancer who seem to have a clinically early stage disease, but who have not undergone comprehensive staging surgery, and therefore whose true stage of disease is unknown, can be defined as a separate group. There are no strong recommendations based on randomized controlled trials in the management of these patients in the period after surgery. In this article, we asked the question of whether these patients should undergo staging surgery, receive chemotherapy without surgery or whether mere observation is enough.

Standard approach in clinically early stage disease

Of patients with EOC, 25-30% are diagnosed in stage I-II (20-25% in stage I) (3). While serous type and high-grade histology predominate in advanced stage ovarian cancer, non-serous types and grade I-II histology are encountered slightly more frequently at the early stages [15].

The International Federation of Gynecology and Obstetrics (FIGO) proposed comprehensive staging surgery as the standard surgical approach for ovarian cancer in 1985. Staging surgery includes a vertical midline incision, peritoneal cytology, exploration, hysterectomy, salpingo-oophorectomy, omentectomy and pelvic-paraaortic lymphadenectomy. Appendectomy should also be added according to the studies of Ayhan et al. [16,17]. Laparoscopic surgical staging has become feasible in recent years [18-25].

Comprehensive staging surgery in ovarian cancer is recommended, but some patients with clinically early stage disease do not undergo staging [26]. For example, in a study by Skirnisdottir et al. [27], lymphadenectomy was included as part of the standard surgical procedure in 20 of 113 patients with early stage ovarian cancer. In another study, Trimbos et al. [28] reported that only 53% of patients with early stage ovarian cancer underwent comprehensive staging surgery. No apparent suspicion of malignancy during surgery, or technical deficiencies such as the absence of frozen section examination or the absence of a specialist surgeon for advanced surgery procedures may be common reasons for not performing comprehensive staging surgery. Staging surgery may be considered more likely if an expert surgeon performs the operation. It has also been shown

that patients operated by a gynecological oncologist have longer survival [29].

In general, these patients are diagnosed with ovarian cancer after surgery without staging. The most frequently omitted steps of staging surgery are the removal of retroperitoneal lymph nodes and getting biopsies from the peritoneum [28]. These patients may be considered as having undergone incomplete surgery, therefore performing complementary surgery for staging is an option. On the other hand, surgery may be considered unnecessary because of the likelihood that the clinically early appearance of the disease is indeed correct. The risk of complications of comprehensive staging surgery and the additional stress of the second operation are some of the disadvantages. Some patients truly have limited disease in the ovary and surgery may be unnecessary [30-33], but it is undetectable without comprehensive staging surgery because there is no diagnostic method to detect occult metastases. The surgical option involves the possibility of an unnecessary surgery while the observation option involves an upstaging risk.

Risks of surgical staging

A comprehensive staging surgery carries various risks such as bleeding and transfusion, gastrointestinal or urinary tract trauma, nerve damage and anesthesia complications. Postoperative complications include infection, lymphedema, lymphocytes, deep venous thrombosis, and pulmonary embolism. In addition, repeated operations may cause stress in the patient. Tam et al. [34] reported 44% lymphocyst formation in patients undergoing pelvic lymphadenectomy. In a recent study evaluating 366 patients, Kuroda and colleagues reported that the cumulative incidence of lower limb lymphedema was 23.1% at 1 year, 32.8% at 3 years, and 47.7% at 10 years post-surgery [35]. Additionally, high body mass index ($\geq 25 \text{ kg/m}^2$), pelvic plus paraaortic lymphadenectomy, and lymphocyst formation were independently associated with lower limb lymphedema. The major morbidity rate associated with the staging surgery procedure was 7.4% according to Snider et al. [36].

Occult metastasis risk

Early stage disease has a latent risk of metastasis and the rate does not seem to be low according to several studies on this subject in literature [30-33]. Visual assessment is inadequate for the detection of micro metastases on the diaphragm, omentum, or lymph nodes. The detectability of occult metastases in positron emission tomography (PET) or magnetic resonance imaging is very poor. In the literature, PET sensitivity for lymph node metastasis is reported between 0 - 90% [37-42]. For metastases below 4 millimeters, sensitivity is too low (~12%) [41].

Staging of the patients with clinically early stage shows that up to 30% are in advanced stage. Garcia et al. [31] found that 29% of patients with clinically early stage who had complete surgical staging had a more advanced stage. Young et al. [30] stated that 31% of these patients were upstaged at the end of the surgical procedure. Ayhan et al. [32] reported an upstaging rate of 31%. In their study, the most common cause of upstaging was lymph node involvement (41%). After performing multivariate analysis, they found that grade 3 cancer, CA 125 >500 , and positive ascites cytology were independent risk factors for

upstaging. In their review article, Klepp et al. [43] reported that the mean incidence of lymph node metastases in clinical stages I-II EOC was 14.2% (range 6.1-29.6%), 7.1% of which were only in the para-aortic region, 2.9% only in the pelvic region, and 4.3% both in the para-aortic and pelvic regions. In a study of the occult metastasis ratio, Arlene et al reported that one-third of the patients with ovarian cancer without gross spread beyond the ovary were upstaged following comprehensive surgical staging [31]. According to literature data, 1 out of 3 patients with clinically early stage disease have widespread disease.

The National Comprehensive Cancer Network (NCCN) guide states that repeat surgery for staging or direct adjuvant chemotherapy are viable options in these patients [44]. There is no suggestion as to which patients are more suitable for which option. It is understood that a patient-based approach should be adopted, considering the benefits and disadvantages of the reoperation or adjuvant chemotherapy. The real stage of disease in the adjuvant chemotherapy approach is unknown. Some patients may have been administered unnecessary chemotherapy due to unknown stage of disease because chemotherapy is not necessary if the disease is FIGO stage 1A and low grade histology [44]. In fact, over-treatment and under-treatment are prevented by reoperation.

Role of chemotherapy in early stage ovarian cancer

In the ACTION (Adjuvant Chemotherapy in Ovarian Neoplasm) multicenter trial, 448 patients with early stage ovarian cancer (FIGO stage I-IIA) were randomly assigned after surgery to adjuvant chemotherapy or to observation [45]. Recurrence rates were lower in the adjuvant chemotherapy arm. Adjuvant chemotherapy improved recurrence-free survival but not overall survival. In this trial, chemotherapy provided better survival than observation in patients who could not undergo complete staging. This may be due to undetermined residual disease. The subgroup analysis performed in this study shows that chemotherapy is unnecessary in patients who have complete staging and the benefit of adjuvant chemotherapy appears to be limited to patients with non-optimal staging.

There is a limited number of studies evaluating the survival rates of these approaches. Le et al. [15] compared patients with early stage ovarian cancer who did not undergo surgical staging with those who underwent surgical staging. The recurrence rates in patients undergoing staging surgery were lower (10% vs 28%, $P=0.036$), although they had less adjuvant chemotherapy (36% vs 43%). Authors indicated that all clinically early-stage ovarian cancer patients should be considered for comprehensive staging surgery prior to further treatment. In the study of Le et al. [15], better survival was shown in the re-operation approach. In their study, unstaged patients had greater recurrence and lower overall survival rates, despite increased rates of chemotherapy.

Conclusion

There are no strong recommendations for the management of unstaged patients with apparent clinically early ovarian cancer. There is little conformity between the clinical evaluation and surgical stage in early stage ovarian cancer. Approximately one third of these patients are found to have a more advanced stage if they are operated on. Re-operation for staging seems to have a survival advantage according to several

studies. Chemotherapy should be given to patients who cannot be re-operated. Our opinion is that observation is not an appropriate option in these patients.

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Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: <http://www.nlm.nih.gov/citingmedicine>