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BASIC PRINCIPLES IN SURGICAL TREATMENT
OF GYNECOLOGIC MALIGNANCIES

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Summary

In the treatment of gynecologic malignancies surgery represents a cornerstone of gynecologic oncology. Surgery is important to establish the definitive diagnosis, to define the extent of disease and to eliminate the tumor according to the type and localization. The most frequent tumors among gynecologic malignancies are cervical, endometrial and ovarian cancer. Actual surgical approach in early cervical cancer with microscopic extension includes conservative techniques, in the first place the use of conisation. In the same group of patients but with fulfilled reproductive activities, hysterectomy is recommended. Radical surgery could be applied in invasive cervical cancer staged IB1 to IIA. Surgical treatment in the advanced stage of cervical cancer could be exerted exclusively in controlled trials as a part of multimodal treatment.

Endometrial cancer still remains incompletely defined in the extension of surgical procedures. Namely, lymphadenectomy in patients with endometrial cancer according to the low rate of lymphatic dissemination is not completely accepted in hospital daily practice. Furthermore, the increasing use of minimal invasive surgery transforms our way of thinking, especially in the case of endometrial cancer. Ovarian cancer still remains an unresolved diagnostic problem with negative implication in the treatment efficacy. About two thirds of patients are in advanced stage at the time of their first surgery, primarily for the lack of a high effective screening test as well as unknown pathophysiology in early ovarian cancer development. In early ovarian cancer comprehensive staging should be done, while in patients with advanced disease standard approach should include maximal effort in surgical cytoreduction.

KEY WORDS: *ovarian cancer, endometrial cancer, cervical cancer, surgery, staging*

TEMELJNA NAČELA KIRURŠKOG LIJEČENJA ZLOĆUDNIH GINEKOLOŠKIH NOVOTVORINA

Sažetak

Kirurški tretman malignih novotvorina ženskog spolnog sustava predstavlja početak i osnovu svakog onkološkog liječenja. Kirurški je zahvat, naime, od temeljne važnosti pri postavljanju konačne dijagnoze, određivanju stadija bolesti, kao i za uklanjanje tumorske mase tijekom prvog operacijskog zahvata sukladno lokalizaciji i vrsti malignoma. Najčešću pojavnost malignoma ženskih spolnih organa nalazimo na cerviksu, endometriju i ovariju. Suvremeni kirurški pristup liječenju ranog stadija - mikroskopskog raka vrata maternice uključuje konzervativne zahvate u smislu konizacije. U slučajevima gdje je reprodukcija završena može se posegnuti za histerektomijom. Radikalna kirurgija predstavlja metodu izbora u klinički invazivnom obliku bolesti (stadij IB1 do IIA). Kirurško liječenje viših stadija može se rabiti u kontroliranim studijama u sklopu multimodalnog liječenja. Rak endometrija i dalje ostaje u određenom smislu nedovoljno definiran u smislu opsežnosti samoga kirurškog zahvata. Naime, limfadenektomija kod bolesnica s rakom endometrija s obzirom na relativno nisku stopu limfogenog rasapa i dalje predstavlja kamen spoticanja u kliničkoj praksi. S druge strane, sve opsežnije uvođenje endoskopske kirurgije otvorilo je nepovratni put ka prihvaćanju operativnih zahvata s minimalno invazivnim tehnikama. Rak jajnika još uvijek predstavlja veliki dijagnostički i terapijski problem. Kako ne postoje široko primijenjeni učinkoviti testovi probira, bolest se u dvije trećine bolesnica otkriva tek u uznapredovaloj fazi s posljedičnom visokom stopom smrtnosti koja premašuje zbroj smrtnosti svih preostalih ginekoloških malignoma. U bolesnica s naiz-

gled ranim stadijem bolesti potrebno je učiniti sveobuhvatni kirurški zahvat radi određivanja točnog stadija bolesti, dok u bolesnica s uznapredovalom bolešću standardni pristup uključuje optimalnu kiruršku citoredukciju.

KLJUČNE RIJEČI: *rak jajnika, rak endometrija, rak vrata maternice, kirurgija, određivanje stadija*

INTRODUCTION

In the treatment of gynecologic malignancies surgery represents a cornerstone of gynecologic oncology. Surgery is important to establish the definitive diagnosis, to define the extent of disease and to eliminate the tumor according to the type and localization. The unique training of gynecologic oncologists in the comprehensive management of gynecologic cancer positions them to serve as the captain of a patient's journey through cancer care. Many other physicians including primary care, obstetricians and gynecologist, anesthesiologist, radiologist, cytologist, pathologist, medical oncologist and other will pass by the examination table, operating room or bedside during screening, diagnosis, initial treatment, management of recurrent disease or palliative care of woman with gynecologic cancer (1). Regardless, it remains the obligation of gynecologic oncologist to promote cooperation and congregate these influences together at one table to promote the common goal – better quality of patients care with better treatment results. Surgical approach in the field of gynecologic oncology, as mentioned above, represents in most cases the first step in the patient treatment and we discuss the actual basic surgical principle in the treatment of cervical, endometrial and ovarian cancer.

CERVICAL CANCER

Actual treatment of cervical cancer, microinvasive and frankly invasive, involve appropriate management for both, the primary lesion and potential sites of metastatic disease. Both surgery as well as radiation therapy may be used with similar results in lower staged group as FIGO stage I or early stage IIA disease. Surgical treatment in advanced stage of cervical cancer FIGO III/IV could be exerted exclusively in controlled trials as a part of multimodal treatment.

Microinvasive carcinoma of the cervix

The term microinvasive carcinoma of the cervix was introduced by Mestwerdt (2) in the German literature in 1947. The author suggests that 5 mm was the deepest penetration acceptable in the term of microinvasive disease. In the last 50 years, there was a lot of debate about the terminology as well the choice for optimal treatment recommendation.

The actual FIGO recommendation was defined in 1985 and included measurements in the definition of stage IA disease for the first time (3). The new definition stated that stage IA was a preclinical form of cervical cancer. The diagnosis of this stage disease is possible only by microscopy. The stage IA is subsequently more precisely defined in 1994. The FIGO Committee defined stage IA1 as a tumor that invaded to a depth of 3 mm or less, whereas stage IA2 referred to a tumor that invaded to a depth greater than 3 mm, up to 5 mm. In both substages, IA1 and IA2, the horizontal spread should not exceed 7 mm. The presence of lymph vascular space invasion was not included as a part of the definition. Namely, LVSI does not change the stage of the disease, but has determined impact on treatment modalities.

Although the microscopic invasion in cervical carcinoma stage IA1 and IA2 is possible to identify in punch biopsy, definitive diagnosis of microinvasion can be made only in conus specimen obtained by conisation or hysterectomy.

In stage IA1, conisation as a surgical procedure take the place of diagnostic and in the same time curative procedure for microinvasive cervical cancer, especially in the case of desired fertility.

In stage IA1, separate lesions with invasion of 3 mm or less and no vascular space involvement meet criteria for conservative management. The risk of lymphatic spread is minimal, and there is no need for adjuvant lymphadenectomy.

Hysterectomy (extrafascial) as a surgical treatment option is reserved for the patients after completed childbearing.

The presence of risk factors, positive internal margin or the presence of cervical intra-epithelial neoplasia or even microinvasive disease in the postconisation endocervical curettage warrant repeat conisation or amputation of the cervix before definitive treatment planning. Lymph vascular space involvement is uncommon in stage IA1. In our unpublished material, among 160 patients with stage IA1 lymph vascular space involvement was found in 9.4%, while literature review reports an incidence not exceeding 15% (4). The clinical significance of LVSI is controversial and the recommendation can be defined from disregarding the finding to the use of lymphadenectomy as staging procedure for definition of lymph node involvement. At the moment, there is no uniform approach to the management. An attempt is made to distinguish lymph vascular space involvement in the definition of disease extension. In the cases with extensive lymph vascular space involvement pelvic lymphadenectomy as adjunctive procedure to conisation can be performed. However, this procedure carries no clear advantage and benefit for the patients.

Stage IA2 has different treatment recommendation from conservative as conisation to radical hysterectomy and pelvic lymphadenectomy. Lymph node metastases varied in the literature from 0% to 13.8% (5-11). Among reported 262 patients, there were 7.3% nodal metastases, 3.1% of invasive recurrences and 2.3% of dead from disease. In our unpublished material, among 11 patients with cervical cancer stage IA2 treated in Rijeka one patient was treated with radiotherapy, 5 patients with hysterectomy and 5 patients with radical hysterectomy and pelvic lymphadenectomy. All patients are after 5 years alive and disease free.

At the moment, more data are needed for this group of patients to define optimal treatment approach regarding lymphatic spread, possible parametrial spread, risk of recurrence and patient outcome. Our recommendation consists of two categories, one regarding the local process where conisation with a clearly negative margin and without LVSI could be a definitive procedure. Hysterectomy without parametrial dissection should be reserved only for patients with resolved childbearing. The second category includes lymphadenectomy as staging procedure. Laparoscopical dissection of lymph node (12) could be performed as additional procedure to conisation or hysterectomy. In the case of extensive lymph vascular space invasion a safer option may be to perform radical trachelectomy or radical hysterectomy with pelvic lymphadenectomy (13). Exclusively conservative approach in stage IA2 would be completely acceptable when more data regarding risk factors are clearly defined. In medically unfit patients, an alternative treatment option should be used. Radiotherapy has a same outcome results and in the cases of microinvasive disease, intracavitary radiation is sufficient to resolve disease in the cervix.

Frankly invasive cervical cancer

Radical surgery, radical hysterectomy with systematic pelvic node dissection represents an alternative treatment option to radiotherapy with the same survival rate in cervical cancer patients staged IB1 and IIA. In 1994, FIGO Committee recognized the prognostic significance of tumor size and subsequently divide stage IB into stage IB1 with primary lesion 4 cm or less and stage IB2 with primary lesion greater than 4 cm. Patients with stage IB1 cervical cancer as well as patients with disease spread staged as early stage IIA are candidates for radical hysterectomy and pelvic systematic lymphadenectomy. Equal cure rate may be obtained with primary radiation therapy (14). Primary surgery has the advantage of removing the primary disease. At the same time, accurate surgical staging could be performed and it is possible to preserve the ovaries. All patients with radical hysterectomy and pelvic node dissection will not be exclusively treated only by surgery, and radiotherapy should be applied in those with identified risk factors. In this group of patients, status of lymph nodes, size of primary tumor, depth of stromal invasion, lymph vascular space invasion, parametrial extension, histologic cell type and close vaginal margins are recognized as major prognostic factors.

A significant part of patients in stage IB1 to IIA have positive bulky nodal metastases. In these patients, the best prognosis is obtained using radical surgery with complete node dissection and adjuvant radiotherapy. The prognosis in

this group of patients is converted to that of nodal micrometastases (15). In addition, patients with a cervical cancer diameter larger than 4 cm (stage IB2) show a higher relapse rate in the group treated only with radiotherapy (30%) compared to those treated with radical surgery and subsequently with radiotherapy (20%) (14). Irrespective of previously mentioned, the optimal treatment recommendation for patients stage as IB2 is controversial. Properly randomized trials are necessary to determine the best approach by measurement a patient cure rate, and also their quality of life.

In patients with primary tumor larger than 4 cm (Stage IB2), including patients staged IIA, a preferred option in the Department of OB/GYN in Rijeka is primary radical hysterectomy with systematic node dissection subsequently treated by postoperative adjuvant radiotherapy with or without chemotherapy (chemoirradiation) depending on the operative finding.

ENDOMETRIAL CANCER

Primary treatment of endometrial cancer includes surgery, which represents for 92 to 96 per cent in everyday clinical practice. At the time of surgery, peritoneal cytologic sampling with exploration of the abdomen, palpation and biopsy of any suspicious lesion including suspicious lymph node should be performed. Basic surgery includes hysterectomy and bilateral salphingo-oophorectomy. Although the addition of lymphadenectomy is necessary for proper staging (16,17), its use is still controversial, especially in stage I endometrial cancer. Some authors claim a survival benefit, because they found a higher endometrial-cancer-specific survival rate than in reported series of patients treated with total abdominal hysterectomy and pelvic radiotherapy on indication (18,19). Lymphadenectomized patients in most series are younger, and age as a major prognostic factor could significantly influence a survival rate. Fore surgical stage I patients the risk of pelvic nodal metastases has been shown to be less than 10% (20). Theoretically, the patient undergoing thorough staging, ideally with a bilateral pelvic and lower paraaortic lymphadenectomy might be at low risk for pelvic sidewall recurrence in the absence

of lymph node metastasis. A pelvic sidewall disease when undetected and untreated could contribute to preventable mortality in this patient population. The major risk of recurrence within the pelvis for such patient, therefore, is to the vaginal vault, where such disease would be treatable with a high probability of local control and, presumably, cure. Namely, rare pelvic recurrences are found in high risk patients undergoing therapeutic pelvic lymphadenectomy and either no radiotherapy or brachytherapy alone in the absence of lymph node metastasis (19, 21-24).

The introduction of laparoscopy in the surgical treatment of endometrial cancer patients has been reported to provide the exact staging with a shorter hospitalization, an earlier recovery, and an improved quality of life (25, 26). At the moment, a randomized phase III trial with inclusion of 2500 patients is to be conducted by the Gynecology Oncology Group. Meanwhile, there is no evidence for prohibiting laparoscopic surgery in patients with endometrial cancer (12).

OVARIAN CANCER

Ovarian cancer includes various types of malignant tumors, but we discuss a surgical approach to epithelial ovarian cancer accounting for more than 90% of all ovarian malignancies.

The FIGO staging system is based exclusively on findings at surgical exploration and examination of surgical specimens by histology and cytology. A choice for possible subsequent adjuvant treatment is determined by the stage of disease.

Early ovarian cancer

The primary treatment for apparent early stage epithelial ovarian cancer should include comprehensive staging with midline or paramedian abdominal incision to allow adequate access to the upper abdomen, washing for cytologic analysis, total abdominal hysterectomy, bilateral adnexectomy (salphingo-oophorectomy), resection of infracolic part of the omentum, multiple blind biopsies of the pelvic, paracolic and diaphragmatic peritoneum, systematic dissection of pelvic and paraaortic lymph nodes. Based on the present risk factors (27, 28) and adequate defini-

tion of the disease stage adjuvant therapy would be applied. At the moment, only patients staged as IA or I B, G1 or G2 with histology type other than clear cell will be candidates for further conservative management, i.e. observation.

Advanced ovarian cancer

The majority of women present with advanced intraabdominal disease with subsequently low cure rates. Since the Griffiths' publication of 30 ago (29), the extent of cytoreductive surgery and the amount of residual disease after primary surgery have been considered the most important factor influencing the survival of patients with advanced ovarian cancer. The premise that the absence or low residual disease after primary surgery results in improved 5-year survival rates has held true in a large number of retrospective and prospective publications to date (30-34). Accordingly, the concept of optimal cytoreduction has evolved over time and now generally applies to residual lesions no larger than 1 cm in diameter after primary surgery (Aletti 2006). The principal goal of cytoreductive surgery is removal of the entire primary tumor with resection of all intraperitoneal tumor deposits, i.e. all metastatic disease. If resection of all metastases is not feasible, the goal is to reduce the tumor burden by resection of all individual tumors to the optimum. The relation between residual tumor mass and cure rate is absolutely clear. Patients with small residual, less than 5 mm tumor had u superior survival than those with larger tumor, 1 cm, 1.5 cm or even 2 cm defined as the largest single metastatic residual tumor (30,35)

Several radical procedures including intestinal resection (36-39), splenectomy (40), diaphragmatic resection (41) and hepatic resection (42) have been described as treatments for advanced ovarian cancer with acceptable residual disease. Minimal residual disease is a critical factor determining overall survival and we should not allow ourselves to dismiss this historically consistent observation without strong evidence that we can predict a priori which tumors will not benefit from radical resection. Aggressive surgical effort in patients with advanced ovarian cancer should be a part of standard approach. It should be performed in centers with adequate training and skill levels as well as with sufficient experience in treating such patients.

CONCLUSION

Surgery is the cornerstone in the treatment of early stage cervical cancer, all stages of endometrial and epithelial ovarian cancer. Surgical experience and training in gynecologic oncology subspecialty should have an important impact on the quality of patients care with better outcome. The rational use of surgical procedures in resolving various gynecologic cancers based on actual recommendation is associated with a favorable effect on the risk of postoperative mortality, morbidity and other factors including perioperative patients outcome.

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