

Restaging in gynaecological cancers

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Summary

Regardless of recent technical developments in the scientific arena, stage is still the most important prognostic factor in gynaecological cancers. Surgical staging is performed in all types of gynaecologic cancers except for cervical cancer. Adjuvant therapies that contribute to survival are planned in the light of information obtained from staging procedures. Therefore, necessary information for further therapeutic management should be revealed by the end of surgical staging. A staging surgery that is not completed for any reason will not only deprive the patient of necessary treatments, but can also cause administration of unnecessary adjuvant treatments. This is especially important, given the undesired effects and cost of both chemotherapy and radiotherapy. A particularly relevant case in point is tumours that look like early stage; this is because upstaging up to 30% has been reported in ovarian and endometrial cancers. As for vulvar cancer, clinical staging has been reported to lead to about 15% over-diagnosis in comparison to surgical staging. Thus, the first step in all gynaecological cancers, except cervical cancer, should be to perform surgical staging when possible and unveil all surgical-pathological prognostic factors in the light of data obtained. Accordingly, restaging surgery should be considered in all cases that had incomplete staging. However, care should be taken to evaluate the benefits to be reaped together with the operative morbidity risk associated with the restaging procedure. This will both ensure accurate planning of postoperative treatment and provide a universal standard of approaching cancer patients and their treatments.

Key words: Staging; Restaging; Ovarian cancer; Borderline ovarian cancer; Endometrial cancer; Vulvar cancer; Tubal cancer.

Introduction

Cancer therapy strategies are made after an evaluation of the patient and tumour, using many methods that often include sophisticated technical procedures. For most types of cancer, the anatomic extent to which the disease has spread is probably the most important factor determining prognosis and must be given prime consideration in evaluating and comparing different therapeutic procedures. Staging classifications are based on documentation of the anatomic extent of disease, and their design requires a thorough knowledge of the natural history of cancer. In addition to anatomic extent, the histological classification and histological grade of the tumour may be important prognostic determinants in the classification for staging that may affect choices for treatment.

The clinician's immediate task is to select the most effective course of treatment and estimate the prognosis. This decision and judgment require, among other things, an objective assessment of the anatomic extent of the disease.

The practice of dividing cancer cases into groups according to "stage" arose from the fact that survival rates were higher for cases in which the disease was localized compared to those where the disease had extended beyond the organ or site of origin. These groups were often referred to as "early cases" and "late (advanced) cases", implying some regular progression with time. Actually, the stage of disease at the time of diagnosis may be a reflection not only of extension of the neoplasm, but also of the rate of growth, the type of tumour and of the patient's response to tumour [1].

The staging of cancer is used to analyse and compare groups of patients. It is preferable to reach an agreement on the recording of accurate information on the anatomic extent of the disease for each site because the precise clinical description and histopathologic classification of malignant neoplasms may serve a number of related objectives, such as; selection of primary and adjuvant therapy, estimation of prognosis, assistance in evaluation of the results of treatment, facilitation of the exchange of information among treatment centres, and contribution to the continuing investigation of human malignancies [2].

The principal purpose of the classification of cancer cases by anatomic extent of disease, however, is to provide a method of conveying clinical experience to colleagues worldwide without ambiguity.

The first requisite for approaches to gynaecological cancers is to obtain knowledge about the extent of the disease. All gynaecological cancers except for cervical cancer are staged surgically. The contributions of surgery to treatment are staging, debulking and providing chance to estimate the pathological risk factors that are not included in parameters that determine the stage. It must be remembered that staging itself is curative at early stages. Since one of the primary treatment alternatives in cervical cancer is radiotherapy, clinical staging is used. The first step in all cancers,

except for cervical cancer, should be sufficient surgical staging, when and wherever possible. However, surgical staging may sometimes be inadequate in the first approach; therefore information expected from staging surgery cannot be obtained. The main reasons for these inadequate operations are inexperienced surgeons or insufficient knowledge about the required skills and procedures. Being unable to discriminate between malignant and benign cases preoperatively is another reason for incomplete surgical intervention, and emergency cases where there is no time for evaluation of possible malignancy, as in some ovarian cysts, is the last and the most acceptable reason.

In these cases, which will be explained in detail in the following parts, staging of the patient by re-operation should be considered. This “restaging” procedure is a reality that every gynaecologic oncologist is often being faced with.

Incomplete staging

Surgical staging is used in all cancers, except for cervical cancer, to identify the extent of disease. In the staging system reported by FIGO, sites where the disease has the potential for spread are stated and it is recommended to subject these sites to a standard examination [2]. Surgical staging procedures in general include assessment of local invasion, regional metastasis and distant metastasis [2, 3]. FIGO staging systems demonstrate in detail which stage is indicated by affection of which sites. The histopathological condition of these sites should be thoroughly examined in surgically staged cancers.

The experience of the surgeon and his/her knowledge on gynaecological cancer and its metastasis patterns are very important in surgical staging procedures. Thus, in a study carried out by Munoz *et al.* on 785 patients, only 10% of patients described as possible Stage I and II, 71% of women in Stage III and 53% of those in Stage IV had benefited from proper staging and treatment. It was found that the primary reason for incomplete staging was not performing lymphadenectomy and not identifying the histological grade [3]. In a study by McGowan *et al.* it was reported that staging was properly performed in 97% by gynaecologist oncologists, 52% by obstetricians and 35% by general surgeons in cases that underwent surgery due to ovarian cancer [4]. The situation is similar in other gynaecologic cancers.

Another condition associated with incomplete staging is whether a sufficient number of lymph nodes are sampled in cases in which lymphadenectomy is performed. Although there is no standard for the number of lymph nodes to be extracted, a reasonable number of lymph nodes should be sampled in optimal staging surgery. These reported numbers are in means: 32 (range 17-57) pelvic and 28 (range 15-35) paraaortic in ovarian cancer and 31 (range 20-68) pelvic and 28 (17-57) paraaortic in endometrial cancers [5]. In order to prevent confusion, we find it useful to review incomplete staging and “maximal surgical effort” terminology. Incomplete staging is seen mostly either due to insufficient knowledge and experience of the surgeon and/or pathologist or in case of cancers which are not thought to be malignant in the preoperative period, but are identified incidentally in the postoperative period. On the other hand, maximal surgical effort is related to either failure to complete the operation due to the patient's medical condition or acknowledgment of the lesion to be unresectable by an experienced gynaecologic oncologist. In the latter case, staging may be made, but cytoreduction is not optimal. In this case, restaging is not possible and one of the existing protocols (for instance, neoadjuvant chemotherapy and interval cytoreduction) is applied. In this paper we are going to discuss restaging surgery that aims at revealing the extent of disease in all aspects by re-operating on the cases whose cancer specimen was incidentally identified and those who had incomplete staging due to the surgeon's lack of enough knowledge and experience.

Restaging

Restaging can be defined as completion of incomplete procedures that had to be conducted in primary surgery of the cancer in order to obtain knowledge about the stage of disease. Expectations from restaging are the same as expectations from the primary staging surgery. Advantages and disadvantages of restaging surgery can be presented as follows:

a) Restaging surgery shows whether it is necessary or not to administer adjuvant therapy by revealing the extent of the disease. As a result of this surgery, the patient should be given adjuvant therapy regimes which are known to contribute to survival. Otherwise, since adjuvant therapies do not have any contribution especially in early stages, the patient is protected against unnecessary financial load and side-effects of adjuvant therapies such as chemotherapy and radiotherapy. This is the case in Stage Ia-b, grade 1-2 ovarian cancers, Stage Ia, grade 1-2 endometrial cancers, and lymph node negative Stage I and II vulvar cancers, where surgery is adequate and additional treatment is not given [6-8].

b) A condition interwoven with staging surgery is cytoreduction. In cases where staging is incomplete, cytoreduction is in a sense incomplete, too. In case of cytoreduction which could not be completely accomplished due to surgical inexperience in the first operation, restaging may offer another opportunity for cytoreduction, though there is no primary benefit expected from restaging surgery. Lymphadenectomy, which is another indispensable part of staging surgery, has therapeutic potential in gynaecological cancers and should be performed in restaging procedures if not performed in the former operation.

c) Even if they do not change adjuvant therapy plans, findings obtained in restaging surgery are required in order to obtain prognostic information, to ensure standardization of disease and to follow new developments in treatment, as well as proper categorization of the disease for further academic purposes.

d) Operative morbidity brought about by restaging surgery is an important issue. Rates of operative morbidity cited in studies seem relatively high. Stier *et al.* reported a 33% complication rate following restaging surgery [9]. In a study by Soper *et al.* 53% severe adhesions, 20% large intestine complications and 20% vascular complications requiring sutures were reported in restaging laparotomy [10]. Therefore, benefits gained from restaging surgery and risks should always be considered together.

Restaging in ovarian cancers

Ovarian cancer is responsible for half of the deaths due to cancer in women [11]. Its primary treatment is surgery and the first procedure to be conducted in a case considered to have ovarian cancer is staging surgery. In this standard procedure, all foci that have spreading potential are excised and histopathologically examined to find out the extent of disease. The decision as to whether surgery is curative in itself or adjuvant therapy is needed is given in the light of this information. In general, no additional treatment is needed in cancers up to Stage Ib, grade 1-2, whereas chemotherapy should be applied to lesions at more advanced stages [5]. Additional treatment applied after surgery in ovarian cancer patients having advanced stage disease according to surgical and pathological staging results is shown to have positive contributions on survival [12]. However, in order to decide whether additional treatment is required or not in cases where staging in initial surgery was not complete, restaging surgery should be performed. The reason is that a vast majority of these cases has the opportunity to be saved from additional chemotherapy by restaging, while the rest will benefit from additional treatment. Soper *et al.* studied benefits and morbidity associated with comprehensive restaging laparotomy in patients who had incomplete surgery in the initial staging procedure. It was established that only 17% of cases had proper incisions, 53% had pelvic washes and 37% had omentectomies. Upstaging was observed in nine patients (30%) with comprehensive restaging and six cases (20%) were found to be at Stage III. Two-thirds of the cases that were upstaged were found to have occult metastasis during peritoneal biopsy and lymphadenectomy. It was reported in that study that poorly differentiated and papillary serous lesions had more upstaging characteristics than well-differentiated lesions and other histological types [10]. Young *et al.* performed additional surgery on 100 cases that were found to have Stage I and Stage II disease and established that 28% of the cases who were claimed to be Stage I and 43% of those claimed to be Stage II were at more advanced stages. Upstaging was found in 16% of grade 1, 34% of grade 2 and 46% of grade 3 cases [13]. According to the present findings, cases that are indicated to receive adjuvant chemotherapy should be restaged as well. There are two important reasons; the first one is completion of staging principles and the second is the cytoreduction that can be performed during the procedure. Another issue that should be taken into account at this point is the condition of patients who did not undergo lymphadenectomy. The present findings show that the cases with nodal involvement are resistant to chemotherapy. This last point is another important aspect of restaging surgery that makes cytoreduction possible.

Restaging should also be performed in incomplete surgery of germ cell tumours. In a study carried out in our clinic on 45 pure dysgerminoma cases, three (23%) out of 13 cases who were referred to as Stage I were found to have upstaging (Stage IIIc) in restaging surgery [14]. Although the patient benefits from chemotherapy in advanced stages in terms of survival, cases with early disease (Stage Ia, grade 1 pure immature teratoma and Stage Ia pure dysgerminoma) do not need postoperative adjuvant chemotherapy [15]. Therefore, these cases should be restaged as well.

Restaging in borderline ovarian tumours

Borderline ovarian tumours (BOT) are a group of epithelial ovarian tumours that have a very favourable prognosis. Borderline epithelial ovarian cancer differs from regular ovarian cancer because it is less malignant and is often responsive to surgery. Borderline tumours comprise approximately 15% of all epithelial ovarian tumours. The mean age of occurrence is approximately ten years younger than that of women with frankly malignant ovarian cancer. Borderline ovarian cancer is staged according to the FIGO classification of ovarian cancer. Many clinicians group Stages II-IV together for prognostic consideration. These tumours, as with other ovarian tumours, are difficult to detect clinically until they are advanced in size or stage. As with other ovarian masses, staging is performed surgically. Many sources recommend complete staging if a borderline tumour is found. Current guidelines include biopsy specimens of the pelvic peritoneum (cul-de-sac, pelvic wall, and bladder peritoneum), abdominal peritoneum (paracolic gutters and diaphragmatic surfaces), omentum, intestinal serosa and mesentery, and retroperitoneal lymph nodes (pelvic and paraaortic). While stage may or may not affect future treatment, it is of significant prognostic value and therefore is of value to both clinician and patient. Comprehensive staging is recommended as a part of every operation. In most instances, surgery is curative for patients with confirmed Stage I disease. If the tumour is unilateral and adjacent to normal tissue, unilateral cystectomy can be performed; however, inspection of the capsule for signs of rupture before resection is necessary. If no normal adjacent tissue is present, oophorectomy or salpingo-oophorectomy may be performed. If normal in appearance, biopsy is not required on the adjacent ovary because of the risk of ovarian failure. Another common component of staging is the description of the type of implants, as these have significant prognostic value. In one study, 77% of patients with invasive peritoneal implants also had non-invasive implants [16]. Owing to the high association between surface proliferations and peritoneal implants, the peritoneum must be explored thoroughly when these lesions are discovered. Implants must be evaluated and removed whenever possible.

Comprehensive debulking and staging decreases the chance of a sampling error that could result in an inaccurate diagnosis and prognosis. Patients with Stage I disease confirmed by comprehensive staging have an approximate 15% recurrence rate. The 5-year survival rate for such patients approaches 100%. In patients with Stage II-IV disease, the prognosis is different. In women with serous tumours with non-invasive peritoneal implants, a mean 20% recurrence rate and a mean 7% death rate were found in reported series [17]. Given the excellent prognosis of patients with Stage I disease and its occurrence in women of reproductive age, fertility-sparing surgery is of great interest. In patients diagnosed with Stage I disease who were treated with fertility-sparing surgery of any type, a higher recurrence was found in patients who had a cystectomy (with or without contralateral oophorectomy) as opposed to patients treated with oophorectomy (58% and 23%, respectively). However, only half of these patients underwent complete staging. When comprehensive staging was performed, no statistical difference was found in recurrence in confirmed cases of Stage I disease. Thus, fertility-sparing surgery is an acceptable option in Stage I disease and several reports are available in the literature about the successful treatment of BOTs with fertility sparing surgery and aftercoming births [18]. This again confirms the need for comprehensive staging in all cases [19].

If borderline ovarian tumour is Stage I or if there are implants, or cells that spread from the primary tumour which are not invading the underlying tissue and are removed during the first surgery, there will be no need for additional treatment. If there are invasive implants at surgery, this is a more aggressive form of borderline ovarian cancer [16].

Most of the patients who have a BOT diagnosis are operated on in community hospitals and their staging is usually incomplete. These incomplete staging procedures are often due to the defect of preoperative diagnostic knowledge or surgical skills of the gynaecologist. These patients are referred to gynaecologic oncology centres with their pathology reports and the decision for additional therapy is up to the gynaecologic oncologist.

Restaging should be performed in all patients with serous and mucinous BOTs referred after surgery without accurate surgical staging. Patients with serous BOTs, especially those with micropapillary features, are more likely to be upstaged at a second procedure since extraovarian disease or contralateral ovarian involvement is higher than in mucinous BOTs. If the first surgery failed to provide a thorough evaluation of the abdomen and pelvis or there is a pathology report indicating positive surgical margins restaging is mandatory. Laparoscopy should be considered as an alternative to laparotomy.

Restaging in endometrial cancers

Like ovarian cancers, endometrial cancers are staged surgically. During staging surgery, total hysterectomy is performed, bilateral ovaries and tubas are extracted, bilateral pelvic paraaortic lymph nodes are dissected, peritoneal cytology is obtained, and biopsies of omentum and suspected peritoneal sites are performed. In order for staging surgery to be adequate, appropriate sampling of the above-mentioned sites should be performed. The proper approach in the treatment of endometrial cancer begins with the identification of the disease in the preoperative period. Cases that are known in advance to have endometrial cancer are surgically staged comprehensively. Failure to conduct required examinations in the preoperative period or false negatives from the diagnostic methods used may cause the treatment in endometrial cancer to be limited to hysterectomy only. Thus, diagnosis may be made on postoperative hysterectomy material. In this case, restaging through a re-laparotomy should be performed except for those patients who are considered low-risk with grade 1 or 2 endometrioid subtype, not more than superficial myometrial invasion, tumour size smaller than 2 cm without macroscopic findings of extrauterine metastasis.

Rate of extrauterine metastasis in low-risk endometrial cancer cases is fairly low. Some authors report that hysterectomy could be sufficient in itself, since pelvic node involvement in these cases is less than 5% [20]. However, some points should be known regarding low-risk endometrial cancer patients. In a study carried out on this group of patients by Watanabe *et al.*, pelvic lymph node involvement was reported to be 4.7% and it was claimed in the same study that nodal disease was not correlated with myometrial invasion or tumour size and was correlated with lymphovascular space involvement only [21]. Takeshima *et al.* also investigated the incidence of lymph node involvement in cases without myometrial invasion, reporting that lymph node metastasis was found in four out of 83 grade 1 cases (4.8%). They emphasised that clinical or operative morbidity in case of restaging should be taken into consideration [22]. Although a restaging decision in low-risk patients is made in accordance with prognostic factors such as depth of invasion and grade, this decision should be made at experienced health centres where expert surgeons and pathologists are found and the patient should be informed about the situation. In addition, re-operation for oophorectomy can be considered in low-risk cases having risk of familial ovarian cancer, if not for restaging. In such a case, restaging can also be performed in the same session. If the disease is regarded to be high-risk according to the findings in the hysterectomy material – such as deep myometrial invasion, high grade, clear cell or serous papillary histologic type – then restaging should be performed in these patients and the extent of the disease should be revealed, because risk of extrauterine metastasis in these patients is higher. Patients will also benefit from the additional treatment given after surgical treatment in light of the obtained information. However, if extrauterine disease is not recognized, the result of the treatment is not promising [23]. An important additional point is that adjuvant radiotherapy in patients without extrauterine metastasis does not contribute to survival [6]. In conclusion, accurate revelation of all characteristics of the disease determines the postoperative treatment and ensures proper treatment of the disease without over- or under-treatment.

Restaging in vulvar cancers

Staging of vulvar cancer has been surgical since 1998. Primary treatment is surgery in all patients, when and where possible. The spectrum of surgical treatment ranges from radical local excision and radical vulvectomy to bilateral inguino-femoral lymph node dissection and pelvic node dissection depending on the patient's age, localization and size of the lesion and depth of the stromal invasion.

Incomplete staging in vulvar cancer is generally seen when only the lesion is dissected and lymphadenectomy is not performed or in cases with positive surgical margins. In case of such an incomplete surgery histopathological findings of the dissected lesion should be disclosed. In cases with stromal invasion less than 1 mm the presence of a free surgical margin is adequate and no additional treatment is required. In cases that are found to have invasion of more than 1 mm, it is necessary not only to extract the lesion, but also to assess the condition of the inguinal lymph nodes and thus restaging surgery is obligatory. The most important prognostic factor in vulvar cancer is the presence of positive inguino-femoral lymph nodes. Therefore, whether inguino-femoral lymph nodes are affected or not should be unveiled in all primary lesions that are deeper than 1 mm. The reason is that irrespective of the primary tumour size, prognosis of patients without lymph node involvement has clearly been shown to be better [7, 21]. Five-year survival of patients with negative inguinal lymph nodes was found to be 98%, whereas the rate was 29% in patients who had three or more unilateral or two or more bilateral lymph nodes affected [24]. Likewise, Hacker *et al.* reported a 96% five-year survival rate in patients with negative lymph nodes, 94% in those with one positive lymph node and 80% in those with two or more positive lymph nodes [25]. Therefore, restaging should be performed in these patients and surgery should be completed.

Besides providing prognostic information, lymph node dissection in vulvar cancer also has therapeutic potential. Dissection of inguinal lymph nodes in early stage vulvar cancer is the only and the most important factor that reduces mortality [8]. Stehman *et al.* found inguinal recurrence in six out of 121 cases who underwent inguinal dissection. It is thought that these recurrences are seen in incomplete dissected inguinal or femoral nodes [26]. At present, there is no need for additional treatment except for local excision in unilateral lesions less than 1 mm [8]. Adjuvant therapy is employed in case of multiple inguinal lymph node involvement with high risk of pelvic nodal disease [27]. GOG randomised patients who had more than one positive inguinal lymph node as adjuvant radiotherapy and pelvic node dissection and found that 2-year survival was 68% in the radiotherapy group and 54% in the pelvic node dissection group [28].

In conclusion, accurate staging of vulvar cancer patients provides the patient the opportunity of benefiting from adjuvant treatment on one hand and prevents the patient from receiving unnecessary adjuvant treatment on the other.

Restaging tubal cancers

These are extremely rare cancers and the experience of many physicians on these cancers is fairly limited. Thus, these patients are seldom diagnosed preoperatively [26]. Diagnosis is mostly given accidentally at the end of a condition like tubal ligation or hysterectomy with bilateral salphingo-oophorectomy. The treatment of the concerned patients varies according to stage of the disease. The issue of whether or not administering chemotherapy to a patient is resolved after surgical staging. Therefore, incomplete surgeries associated with tubal cancers may pose problems, as is the case in other cancers. According to common treatment protocols currently in use, adjuvant chemotherapy is not applied in case of limited muscle invasion and negative peritoneal washing and is applied in all stages that are more advanced. Therefore, restaging should be performed in all cases that had incomplete surgery.

Conclusion

At present, the first step in the treatment of all gynaecological cancers is divulgement of the extent of the cancer and all the prognostic factors that can be obtained. Therefore, the primary treatment alternative in all cancer patients should be appropriate surgical staging. Accurate revelation of all aspects of the disease is the distinctive factor in correct post-operative treatment approaches. However, proper standardization for the purpose of comparing various treatment modalities that are still at the stage of clinical studies in gynaecological cancers among centres depends on accurate disclosure of the extent of the disease. Therefore, taking cost-benefit ratio into account in all cases where staging surgery is inappropriately performed, completion of the staging procedure with a restaging procedure should be considered in all patients, when and where possible.

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