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Editorial

Staging Cervical Cancer–Current and Future Perspectives

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Abstract

Cervical cancer (CC) represents the third most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide. Clinical examination is the basis for the FIGO classification. Nodal metastasis in patients with locally advanced CC, together with tumor volume and clinical stage, is the strongest prognostic factor for survival and the most important prognostic factor for disease recurrence together with tumor stage is the para-aortic (PA) nodal status. MRI is the preferred method to assess local spread of cervical tumors. However, PET seems to be more sensitive than MRI for detecting pelvic and PA nodal involvement. Hybrid MRI-PET is an emerging modality that involves no associated radiation exposure and offers the high soft tissue resolution of MRI. Fused images from MRI and PET had higher diagnostic value than PET-CT for detection of metastatic nodes in patients with CC. Surgical staging of patients with locally advanced CC may lead to treatment modification in 20-40% of the patients, resulting in improved survival. In early stage CC, sentinel lymph node (SLN) biopsy is currently under investigation. Although CC is a commonly diagnosed disease among women worldwide, there is still a long way to go until optimal screening, staging and management can be achieved. Large randomized controlled trials are needed to provide more accurate information about the ideal staging procedures and its efficacy and relation with survival rates.

Keywords: Cervical cancer; Staging; MRI

Introduction

Cervical cancer (CC) represents the third most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide [1]. In 2008, across the world, 530,000 new cases were diagnosed with 275,000 deaths [2]. Developing countries carry the biggest burden with approximately 76-85% of CC cases [3]. In Brazil, it was estimated 17,540 new cases of invasive CC for 2012, a rate of 17 cases per 100,000 Brazilian women [4]. Most patients present at diagnosis with locally advanced disease (IB2 - IVA) [5].

In most asymptomatic women, the diagnosis is made as a result of CC screening or incidentally upon pelvic examination. Clinical examination is the basis for the FIGO classification, which is the most widely, used staging system. FIGO determines that clinical staging for CC has advantages, such as: accessibility for low resources setting, easier for assessing locally advanced disease and avoids surgery in women who are not candidates for surgical treatment [6]. Currently, FIGO procedures for staging are limited to colposcopy, biopsy and conization of the cervix. Cystoscopy and proctosigmoidoscopy are recommended if bladder or rectal extension is suspected [7]. The clinical assessment of FIGO classification focuses on determining tumoral extension: tumor size, vaginal and/or parametrial involvement, and bladder/rectum tumoral extension. Complex radiological and surgical staging procedures are not addressed mostly because noninvasive radiographic imaging is not routinely available in low-resource countries; therefore, FIGO system limits the imaging to chest radiography, intravenous pyelography and barium enema. Nevertheless, in the United States, for example, CT, MRI, PET-CT and surgical staging are often used to guide therapeutic interventions for CC stage IB2 or higher. The use of CT, MRI or PET-CT may aid in treatment planning but is not accepted for formal staging purposes [8].

Nodal metastasis in patients with locally advanced CC, together with tumor volume and clinical stage, is the strongest prognostic factor for survival [7,9], and the most important prognostic factor for disease recurrence together with tumor stage is the para-aortic (PA) nodal status [10]. CC can spread by direct extension, by lymphatic or hematogenous dissemination. Direct extension may involve the uterine corpus, vagina, parametria, peritoneal cavity, bladder, or rectum. The most common sites for hematogenous spread are the lungs, liver, and bone; bowel, adrenal glands, spleen, and brain are less frequent sites.

Local expansion to the uterine corpus, vagina, and parametria is commonest, thus, the cervix and entire vagina should be inspected and palpated to identify overt tumors or subepithelial vaginal extension. Vaginal extension is diagnosed with visual inspection. Tumor size and parametrial involvement are best assessed by rectovaginal examination. All suspicious lesions should be confirmed by biopsy. The pathological diagnosis should be made according to the WHO classification based on a surgical biopsy [6,11].

FIGO clinical staging appears to perform best for macroscopic or late stage disease, but less well for stages that depend largely upon assessment of tumor size or local spread [12]. Based on data from over 13,000 women with CC, the correlation between clinical staging and surgicopathologic findings reached 90% or higher only for stage IA1 (microscopic disease) and stages IIIB and IVA (tumor extends to pelvic sidewall, hydronephrosis, or bladder/rectal invasion) [13]. For other stages, the correlation between clinical and surgical stage ranged from 66 to 83%.

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Due to limitations of clinical staging, evaluation with imaging studies and surgical procedures are routinely used to detect the presence of lymph node and distant metastases. Therefore when available, results of these additional testing modalities should be used for planning treatment [11].

If imaging is used, MRI is the modality of choice. MRI is considered the reference complementary imaging modality as it is superior to CT scan for tumor extension assessment and equal to CT scan for nodal involvement assessment. Both MRI and CT have low sensitivities for nodal involvement [11].

For women who are surgical candidates based upon clinical staging, data suggest that tumor size can be determined more effectively with MRI than clinical examination. A prospective study with 208 women underwent MRI and CT prior to surgery, most with stage IB disease. MRI correlated more closely with surgicopathologic findings than CT or physical examination. All three modalities overestimated tumor size. This is important as overestimation of tumor size in surgical candidates would not change treatment or prognosis, while underestimation of size would potentially triage a patient to surgical excision when chemoradiation (CRT) would be the best option [14].

The presence or absence of parametrial involvement (PMI) is also of importance for determining whether patients are candidates for surgical treatment. There is conflicting data if imaging studies are better able to detect PMI than clinical staging. A prospective multicenter study of 172 women with CC who were clinically staged as IB or higher underwent CT and MRI prior to surgery [12]. Detection of stage IIB or higher was poor for all approaches, but imaging studies performed better than clinical staging (clinical staging - sensitivity: 29% and specificity: 99%; CT - 42 and 82%; MRI - 53 and 74%, respectively). If an imaging study is used for parametrial assessment, MRI should be the modality of choice. MRI was found to be superior to CT for evaluation of PMI in a meta-analysis of 57 studies [15,16].

A recent study evaluated 190 stage IB1 CC patients with clinically visible lesions who had undergone radical hysterectomy and preoperative MRI. Patients were stratified as low risk when tumor size was < 25mm and no PMI was evident in the MRI. A high correlation between MRI and pathologic findings was seen in the patients stratified by risk [17].

Pelvic nodal involvement is noted in 30-50% of affected women but, whatever the stage of disease; pelvic nodes are routinely included in radiation fields and receive a local boost when necessary. PA nodes are involved in 10-25% of patients; systematic extension of radiation fields to this area is associated with increased morbidity, therefore it should be considered only if PA nodal spread is either highly likely at imaging or proven by pathological examination [7,18].

There are few data analyzing the use of PET-CT for the evaluation of tumor size or local spread in CC. PET has been reported to have sensitivity and specificity of 100% and 90% respectively, but it is still under evaluation, and is being compared with surgical nodal staging [19]. Its value for detection of extrapelvic organ metastasis is notable, but it is also disappointing for recognition of small-volume metastases. Surgical staging could enable the clinician to offer individualized management.

MRI is the preferred method to assess local spread of cervical tumors. However, PET seems to be more sensitive than MRI for detecting pelvic and PA nodal involvement (PA sensitivity of 38-86% and specificity of 75%) [10,20]. CT and MRI cannot differentiate metastatic nodes from hyperplastic nodes of similar size and PET has scarce value for detection of local spread because of limited spatial resolution. Hybrid MRI-PET is an emerging modality that involves no associated radiation exposure and offers the high soft tissue resolution of MRI [10]. Fused images from MRI and PET had higher diagnostic value than PET-CT for detection of metastatic nodes in patients with CC [7,21].

Surgical pelvic and PA nodal staging are optional. When PET-CT shows uptake in PA nodes, and particularly if uptake is present in both pelvic and PA regions, extension of radiation fields to PA area is indicated without histological analyses. If isolated PA uptake is identified, surgical staging should be indicated to avoid mismanagement due to a false-positive result.

The false-negative proportion rate of PA nodes on PET-CT is 5-17% mainly attributable to non-detectable nodal disease (<5 mm). Laparoscopic staging surgery could be indicated taking into consideration the potential morbidity is low. The pattern of PA dissection is important because it could affect the therapeutic strategy and lymphadenectomy-related morbidity. Common iliac involvement might need prophylactic PA irradiation. Patients with definite uptake in the pelvis, the rate of false-negative PA involvement are 22%. Thus, staging surgery in these patients has considerable benefits because it allows accurate adaptation of treatment (extension of radiation fields to the PA area). In patients without pelvic node uptake, the rate of false-negative involvement in the PA region is much lower (9%) and the benefit of surgery is debatable [7].

Lymphadenectomy can be performed via laparotomy or laparoscopy through a transperitoneal or extraperitoneal approach. Morbidity rates of laparotomy range from 10-19% and the extraperitoneal approach is superior in terms of reduced morbidity. However, the extraperitoneal laparoscopic approach substantially reduces perioperative morbidity and incidence of radiotherapy-induced complications [10,22,23].

Recent studies have shown that surgical staging of patients with locally advanced CC may lead to treatment modification in 20-40% of the patients, resulting in improved survival [10,24]. The effect on survival of surgical or conventional radiological (CT or MRI) staging was investigated in 685 patients from three phase 3 trials (GOG 85, GOG 120 and GOG 165) of chemoradiation therapy. The data suggest an improvement in survival of patients undergoing surgical staging, although those results should be cautiously interpreted: data were gathered from three different trials, the distribution of radiological and surgical staging was unbalanced among trials (GOG 85 and GOG 120 required pretreatment surgical sampling of PA nodes, whereas surgical staging in GOG 165 was optional). Patients of GOG 85, GOG 120 and 29 patients of GOG 165 (n = 555) with histologically proven negative PA nodes were compared with 130 patients from GOG 165 who were staged clinically with negative PA nodes, which suggested that in GOG 165 the true effect of surgical staging was not completely assessed [7]. Women with locally advanced CC with low volume PA nodal disease treated by extended field CRT have

disease-free survival similar to those without such PA spread and managed by pelvic radiation alone. In a prospective series recently published, the subgroup of patients who were found to have a small PA metastasis (<5 mm) after laparoscopic staging surgery and were then treated with extended-field CRT, the prognosis was similar to that of patients without PA metastasis. Therefore, screening these patients, combining PET and staging surgery should be the ultimate target for cure [7].

In early stage CC, sentinel lymph node (SLN) biopsy is currently under investigation. This technique seems to be a feasible method of lymph node assessment with high detection rate. Some benefits of this approach are: triage patients from surgery to combined CRT, avoidance of full lymphadenectomy, detection of key nodes in atypical location and detection of micrometastases (< 2mm). The avoidance of full lymphadenectomy offers less surgical morbidity as was shown in SENTICOL 2 (ESGO 2013) study and it is a secure procedure in terms of false negative rate [25]. Detection of nodes in atypical location is an important issue because these sites could be missed during the full lymphadenectomy. Rob et al showed that the SLN could be placed in less common fields in 10% of the cases. A literature review including 831 women who underwent lymphatic mapping and SLN detection as part of their CC therapy reported that a SLN was identified in 90% of the cases with an overall sensitivity for metastatic disease of 92% [26].

SLN biopsy appears to perform better than imaging studies. This was illustrated in a meta-analysis of 72 studies including 5042 women with CC that evaluated several approaches, and found that the sensitivity and specificity for the detection of lymph node metastases for various approaches were: SLN biopsy - sensitivity: 91% and specificity: 100%; PET - 75 and 98%; MRI - 56 and 93%; CT - 58 and 92%, respectively [26].

Although CC is a commonly diagnosed disease among women worldwide, there is still a long way to go until optimal screening, staging and management can be achieved. A broad understanding of the pathogenesis and carcinogenesis can assist technological advances, incorporation of new imaging studies and surgical procedures, therefore improving clinical evaluation and development of a more precise and effective approach to treatment of this disease. Large randomized controlled trials are needed to provide more accurate information about the ideal staging procedures and its efficacy and relation with survival rates.

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