Gynecologic Oncology Reports 25 (2018) 115–121

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Review article

Imaging and cancer of the cervix in low- and middle-income countries

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ARTICLE INFO

Keywords:
Cervical cancer
Staging
Ultrasound
Computed tomography
Low and middle-income countries

ABSTRACT

Cervix cancer is the fourth most common cancer globally but the second most cancer in women in resource-limited countries. It has remained a clinically-staged neoplasm as per the International Federation of Gynecology and Obstetrics staging classification. As the imaging machines are becoming more available worldwide, the resource-stratified guidelines recommended the inclusion of imaging whenever possible to guide treatment planning. In this report, the utility of imaging in low- and middle-income countries for diagnosis and treatment of cancer of the cervix will be reviewed.

1. Introduction

There are extraordinary disparities in the diagnosis and treatment of cancer of the cervix. Mortality is 18 times higher in low and middle income countries (LMIC) than it is in wealthy nations (Ferlay et al., 2015). The absence of screening programs results in a dramatically higher incidence in sub-Saharan Africa, Central and South America, the Caribbean, Southern Asia and parts of Eastern Europe. Cervix cancer remains a leading cause of death among women with 530,000 new cases annually and 270,000 deaths globally (Centers for Disease Control and Prevention, n.d.). There has been little new progress in the early detection and treatment of cancer of the cervix. The National Cancer Institute (NCI) alert that indicated a survival improvement with the addition of cisplatin-based chemotherapy to radiation therapy was published > 19 years ago (Morris et al., 1999; Rose et al., 1999). With access to care, many women can be cured without advanced technologies. An almost century-old study demonstrated survival rates of 75% for women with early-stage cervix cancer (Regaud, 1932). This determination was made well before the advent of cross-sectional imaging. Cervix cancer has remained a clinically-staged neoplasm because most or many patients do not have access to imaging and accurate assessment of the extent of disease. The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) have published resource-stratified guidelines that indicate the highest level of care, including imaging, should be provided whenever possible (Chuang et al., 2016; Network NCC, 2016). In this report, we will describe the utility of imaging in low- and middle-income countries for diagnosis and treatment of cancer of the cervix.

2. History of staging of cervix cancer

Nearly one hundred years ago it was recognized that staging systems should be valid, reliable, and practical. Cervix cancer staging had its origins in the Radiological Sub-Commission of the Cancer Commission of the Health Organization of the League of Nations (Odicino et al., 2008). Drs. J. Heyman (Radiumhemmet, Stockholm), A. Lacassagne (Radium Institute for the University of Paris), and F. Voltz (Munich) argued for information to be collected more consistently. They discussed the necessity of a uniform method to describe the extent of disease. These recommendations, adopted and published in 1929, became known as the League of Nations Classification for Cervical Cancer; however, widespread use did not immediately occur (Tropé et al., 2001). Annual Reports were published in the ensuing years, and in 1958 the International Federation of Gynecology and Obstetrics (FIGO) became the official patron of the Annual Report. In 1976 the American Joint Committee for Cancer Staging and End Results Reporting accepted the FIGO stage grouping for gynecological cancers (Annual Report on the Results of Treatment in Gynecological Cancer, n.d.). There have been eight changes to the FIGO staging system since its adoption 60 years ago with the most recent update in 2009.

3. Rules for staging of cervix cancer

Cervix cancer continues to be a clinically-staged disease as a result

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https://doi.org/10.1016/j.gore.2018.07.001
Received 18 May 2018; Received in revised form 1 July 2018; Accepted 10 July 2018
Available online 20 July 2018

of the lack of surgical and radiographic expertise in areas of the world where cervix cancer predominates; however, efforts continue in advancing these modalities (Pecorelli et al., 2009). The optional staging techniques are palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and x-ray examination of the lungs and skeleton. A visible lesion confined to the cervix, a microscopic lesion greater than IA1 or IA2, or both and < 4 cm, is stage IB1. Inaccuracies exist between clinical staging and surgical staging in IB and stage II disease (FIGO (International Federation of Gynecology and Obstetrics), 2006). Tumor size has been recognized as an important prognostic factor and is more challenging to assess accurately in advanced-stage disease (Narayan et al., 2003). Cross-sectional imaging has not been endorsed because of its limited availability. If available, these techniques should be utilized to assess the primary tumor and direct treatment. If nodal involvement is discovered, the methodology by which the diagnosis was identified should be noted: pathologic or radiologic. If pathologic details are identified, they are not permitted to change the clinical stage, yet they should be recorded and used to develop an accurate treatment plan. Lymph node metastases strongly impact survival but are not included in the clinical staging system. This is the principle shortcoming of the clinical staging system. Regional lymph nodes include parametrial, obturator, internal and external iliac, common iliac, and presacral. Para-aortic lymph nodes are deemed metastatic, yet many reports document that a subset of these patients can be cured (Grigsby et al., 2001). In a series of 560 patients evaluated by a pre-treatment positron-emission tomography (PET) scan, Kidd et al., describe markedly worse outcomes for lymph node-positive patients. Additionally, patients with para-aortic involvement had a lower survival rate compared to pelvic-only involvement, and all patients with para-aortic involvement had PET avid pelvic lymph nodes. Of the 560 patients, para-aortic involvement was present in 17% and the disease-specific 5-year survival rate in this cohort was lower than 35% (Kidd et al., 2010).

4. Ultrasound in diagnosis in low- and middle-income countries

Ultrasound (US) has been an essential first-line imaging modality in the detection and characterization of gynecological disorders since the advent of real-time ultrasonography in the mid-1970's (Campbell, 2013). Although magnetic resonance (MR) is considered the gold standard imaging modality in the detection, characterization, and local staging of cervical cancer in industrialized nations, the worldwide acceptance of US in the assessment of cervical cancer has significantly increased over the past two decades (Fischerova et al., 2008; Testa et al., 2009; Gaurilcikas et al., 2011). Some relatively recent prospective studies have demonstrated an accuracy of transvaginal or transrectal US comparable to MR. (Epstein et al., 2013; Testa et al., 2014) Ultrasound is fast, widely available, requires minimal patient preparation, and is far more affordable than other imaging modalities. Therefore, it is the most attractive imaging modality for the detection and characterization of cervical cancer in low- and middle-income countries. Transvaginal and transrectal US probes can be positioned in close proximity to the cervix, providing detailed high-resolution imaging of cervical neoplasms (Testa et al., 2009; Gaurilcikas et al., 2011). In a recent European multicenter study of 182 women with early-stage cervical cancer (FIGO IA2-IIA), preoperative transvaginal and transrectal ultrasound examination provided 96% accuracy for tumor detection, with 90% sensitivity and 97% specificity (Epstein et al., 2013).

Cervical cancers generally present as solid, predominantly hypoechoic masses on US relative to the background cervical stroma (Fig. 1-b) (Testa et al., 2014). However, cervical cancers may rarely present as isoechoic or hyperechoic lesions (Testa et al., 2014). It has been suggested that the echogenicity of the tumor may correlate with the histologic subtype of the cervical cancer. In a multicenter study of 55 women with cervical cancer, isoechoic tumors were more commonly seen in adenocarcinomas (13 out of 19 [68%]), whereas hypoechoic tumors were more commonly seen in squamous cell carcinoma (11 out of 15 [73%]) (Epstein et al., 2010). Tumor growth characteristics have been described in the literature based on lesion morphology, with “mushroom” lesions corresponding to an exophytic growth pattern, whereas “ovoidal” or “conical” lesions correspond to an endophytic growth pattern (Testa et al., 2014). An advantage of intracavitary US is the ability to dynamically compress the region of interest during real-time evaluation. Tumors of the cervix have been described as relatively noncompressible on transvaginal or transrectal US examination relative to the normal background cervical stroma (Testa et al., 2014).

Color and power Doppler interrogation frequently demonstrate increased vascularity of cervical tumors compared to the unaffected background cervical stroma (Fig. 2) (Testa et al., 2014). Some investigators have suggested that color Doppler may aid in predicting the aggressiveness of cervical tumors. In a study by Cheng et al., 104 women with early-stage cervical carcinoma (stage IB-IIA) underwent preoperative transvaginal US assessment. Tumors with detectable blood flow had higher histologically proven vascular density, and were associated with higher risk of stromal and parametrial invasion and metastatic lymphadenopathy (Cheng et al., 1999). In a study by Alcazar et al., increased vascularity was found more frequently in squamous carcinoma, moderately or poorly differentiated tumors, large tumors, and advanced-stage tumors (Alcazar et al., 2003).

5. Computed tomography in diagnosis in low- and middle-income countries

Computed tomography (CT) is a widely utilized imaging modality that is accepted as the “workhorse” modality of oncologic imaging. CT is more cost-effective than MR and more widely available worldwide, particularly in developing nations. It can provide a comprehensive evaluation of an oncologic patient with the rapid acquisition of high-spatial resolution images. However, in spite of recent technological developments in intravenous contrast-enhanced CT, the soft-tissue contrast resolution remains inferior to that of MR. (Testa et al., 2014)

Following intravenous administration of iodinated contrast material, the normal cervix demonstrates a variable enhancement pattern that can persist over several minutes (Kaur et al., 1998). Cervical tumors can be either hypoattenuating or isoattenuating to normal cervical stroma after administration of intravenous contrast material. Unfortunately, 50% of stage IB cancers have been described as isoattenuating to normal background cervical stroma, severely limiting tumor detection (Hricak and Yu, 1996). Even large tumors may present as nonspecific cervical enlargement (Testa et al., 2014). However, cervical enlargement in the setting of underlying malignancy can be of prognostic significance; cervical enlargement > 3.5 cm (cm) with an anteroposterior size of the cervix > 6 cm correlates with a poorer outcome (Walsh, 1992; Ogino et al., 1997). In certain instances, large tumors often show a rim of high attenuation with central areas having low attenuation. (Fig. 3). Such low attenuation areas of tumor involvement may be seen as a result of necrosis, ulceration, or reduced vascularity leading to increased conspicuity (Hricak, 1991). Tumors of the cervix frequently obstruct the endocervical canal and distention of the endometrial cavity with blood, serous fluid, or pus (Walsh, 1992).

6. US and CT for evaluation of extent of disease

Sonographic assessment of cervical stromal infiltration is optimally assessed using a transvaginal or transrectal probe. The degree of cervical stromal invasion is a major prognostic factor which directly correlates with the degree of nodal involvement. The degree of cervical stromal invasion can be reliably quantified by transvaginal sonography, with superficial tumor stromal invasion involving < 2/3 of the stroma, and deep stromal invasion involving ≥ 2/3 of the stroma (Epstein et al., 2013). Both transvaginal and transrectal US examination can provide high sensitivity and specificity for the assessment of the depth of