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INVITED REVIEW ARTICLE

The Role of Ultrasound in the Assessment of Uterine Cervical Cancer

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Abstract Uterine cervical cancer is the second most frequent gynecological malignancy worldwide. The assessment of the extent of disease is essential for planning optimal treatment. Imaging techniques are increasingly used in the pre-treatment work-up of cervical cancer. Currently, MRI for local extent of disease evaluation and PET-scan for distant disease assessment are considered as first-line techniques. Notwithstanding, in the last few years, ultrasound has gained attention as an imaging technique for evaluating women with cervical cancer. In this paper, current knowledge about the use of ultrasound for assessing uterine cervical cancer will be reviewed and discussed.

Keywords Ultrasound · Cervical cancer · Staging

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Introduction

Uterine cervical cancer is the second most frequent gynecological malignancy worldwide [1]. The assessment of the extent of disease is essential for planning optimal treatment. The International Federation of Gynecology and Obstetrics (FIGO) recommends a clinical staging system based mainly on pelvic exam, cystoscopy, and rectoscopy [1]. However, this system underestimates or overestimates the actual extent of disease in a significant number of cases [2, 3].

For this reason, imaging techniques are increasingly used in the pre-treatment work-up of cervical cancer [4]. Currently, MRI for local extent of disease evaluation and

PET-scan for distant disease assessment are considered as first-line techniques [5, 6]. Notwithstanding, in the last few years, ultrasound has gained attention as an imaging technique for evaluating women with cervical cancer.

In this paper, current knowledge about the use of ultrasound for assessing uterine cervical cancer will be reviewed and discussed.

Transvaginal/Transrectal Ultrasound for Local Staging of Cervical Cancer

Studies evaluating the role of transvaginal/transrectal ultrasound for staging cervical cancer were reported in early 90s.

Innocenti et al. reported a series of 124 women who were diagnosed as having cervical cancer, comparing clinical staging and transrectal ultrasound [7]. They found that transrectal ultrasound (TRU) had a higher sensitivity than clinical exam for detecting parametrial infiltration (78 % vs 50 %) ($p = 0.06$).

Fischerova et al. compared TRU and MRI in early stage cervical cancer [8]. In a series of 95 cases, they reported that TRU was able to detect more clearly small cervical cancers (<1 cm [3]) than MRI and that TRU was more sensitive than MRI for detecting parametrial involvement (83 % vs 50 %).

Similarly, Testa et al. reported a series of 68 women with cervical cancer, comparing transvaginal sonography (TVS) and MRI for cancer staging [9]. They found that TVS was more sensitive than MRI for identifying parametrial involvement (60 % vs 40 %). But differences did not reach statistical significance.

An interesting paper by Gaurilcikas et al. assessed the ability of TVS to delineate the location and measure the size of early cervical cancer using histology as gold standard [10]. The correlation was high.

More recently, Epstein et al. reported the results of an European multicenter study comparing TVS and MRI for delineating cervical tumor. These results showed that TVS was superior to MRI in both women with and without cone biopsy prior to surgery [11].

Regarding the role of ultrasound for detecting lymph nodes in cervical cancer, Mamsen et al. showed that the sensitivity of this technique is low (23 %) but with an acceptable positive predictive value (71 %) in a series of 109 women [12]. Similar results have been also reported in more recent studies [9, 13].

An excellent paper by Fischerova describes the technique for ultrasound evaluation of women with cervical cancer [14]. A detailed assessment allows measuring the size of the tumor (Fig. 1), to determine the depth of stromal infiltration (Fig. 2), the location of the tumor (Fig. 3), the involvement of parametrium (Fig. 4), bladder (Fig. 5) and rectum (Fig. 6), and even the assessment of pelvic lymph nodes (Fig. 7).

There are some reports about the use of three-dimensional ultrasound (3DUS). Chou et al. compared 3DUS and two-dimensional ultrasound (2DUS) for tumor volume estimation using histology as gold standard [15]. They found that 3DUS was more accurate than 2DUS.

Ghi et al. assessed the role of transvaginal 3DUS for local staging in 14 cases of early cervical cancer [16]. They reported that 3DUS agreed with histologic data in 12 out of 14 cases.

More recently, Byun et al. compared 3DUS, MRI, clinical exam, and surgical staging in a series of 24 women with cervical cancer [17]. They reported that accuracy was higher for 3DUS (67 %) as compared with pelvic exam (62 %) and MRI (41 %).

Transvaginal Color Doppler in Cervical Cancer

Angiogenesis is the production of new vessels in a specific area. It has been demonstrated that angiogenesis is an essential event for tumor growth and progression [18]. Specifically, in cancer of the cervix, angiogenesis has been shown to be an independent prognostic factor [19, 20] and to predict recurrence [21]. Transvaginal Doppler ultrasound allows an in vivo non-invasive assessment of tumor angiogenesis [22] (Fig. 8).

Initial studies assessing blood flow hemodynamics in cervical cancer in the early 90s focused on the main feeding cervical vessels: the uterine artery [23] and the cervical branch of the uterine artery [24]. These studies reported that mean PI in the uterine arteries and cervical

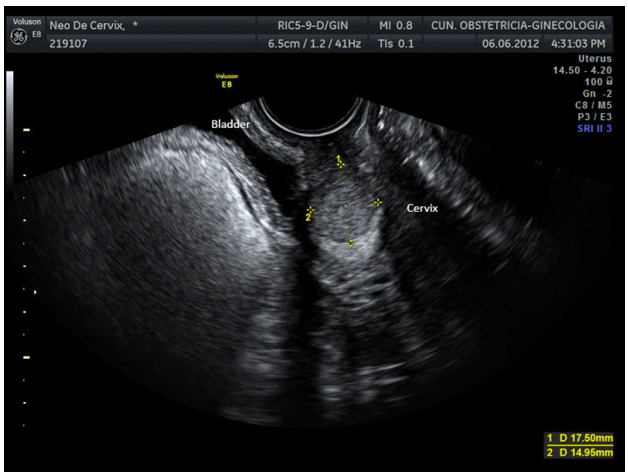

Fig. 1 Transvaginal ultrasound, longitudinal plane, of a small cervical cancer located in the anterior cervix. Size can be measured

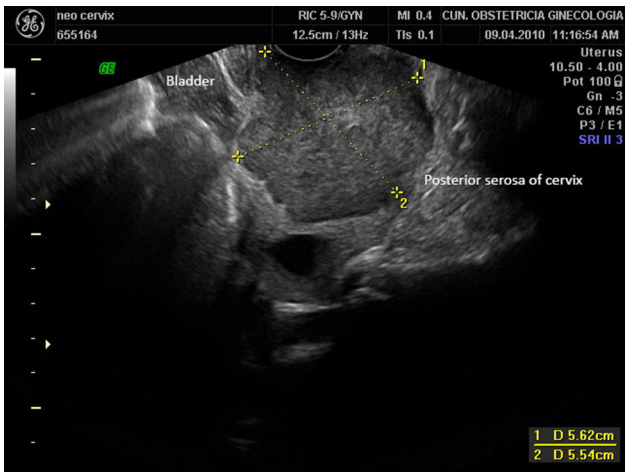

Fig. 2 Transvaginal ultrasound showing a large cervical cancer in longitudinal plane. Deep stromal invasion is suspected. The limits of the lesion are close to cervical serosa

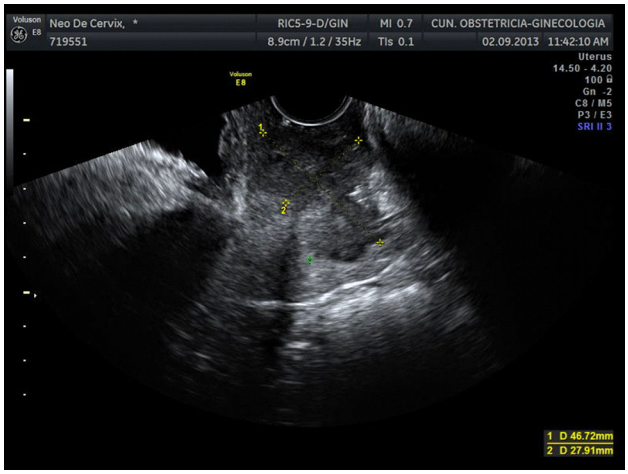

Fig. 3 Transvaginal ultrasound showing a large cervical cancer in longitudinal plane. In this case, the lesion is large and irregular involving both anterior and posterior cervix

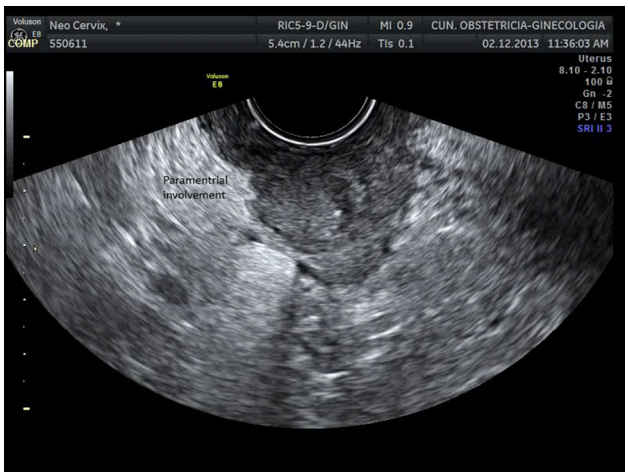

Fig. 4 Transvaginal ultrasound showing a large cervical cancer in transverse plane. Proximal parametrial involvement is suspected as irregularities in cervical limits

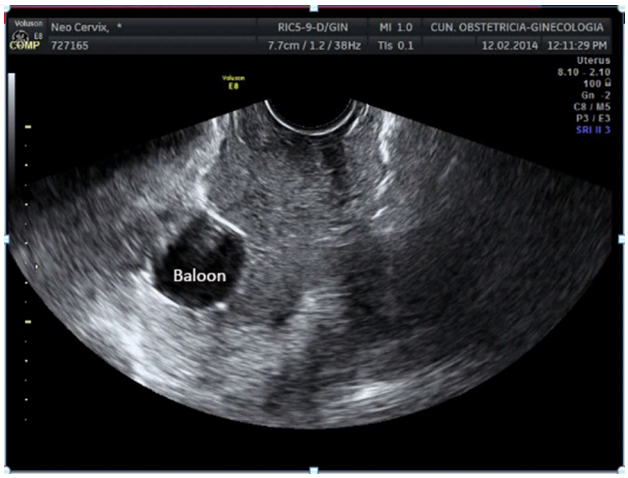

Fig. 5 Transvaginal ultrasound showing a large cervical cancer in longitudinal plane. Bladder involvement is observed. Foley's catheter balloon is seen

arteries of women with cervical cancer was significantly lower than in healthy women.

The first paper analyzing intratumoral vessels in cervical cancer was reported by Hsieh et al. in 1995 [25]. These authors found that 46.2 % of cervical cancers exhibited blood flow color signals as assessed by transvaginal color Doppler sonography. They reported that in those patients with detectable color signals lymph node involvement was more frequent as compared with those without color signals detectable (33 % vs 5.7 %, $p = 0.005$) and this also correlated with a higher cell proliferation index. They did not find differences in tumoral stage, patient's age, clinical staging, histologic type, and DNA ploidy status.

Cheng et al. reported a novel vascular index (VI) for the in vivo assessment of angiogenesis in patients with cervical carcinoma [26]. They evaluated 35 patients with stage Ib-IIa cervical carcinoma by transvaginal power Doppler ultrasound, and using image processor software they developed a vascular index (VI = number of colored pixels/number of total pixels) for each tumor. They reported that this method was highly reproducible and they found that the higher VI the higher tumoral stage, the deeper stromal invasion, the higher lymphovascular space invasion rate, and the higher pelvic lymph node metastases rate. More interestingly, this VI had a good correlation with intratumoral microvessel density as assessed immunohistochemically ($r = 0.586$). Although this paper was the first to demonstrate the correlation between immunohistochemically assessed angiogenesis and power Doppler assessed angiogenesis, the main problem is that the method

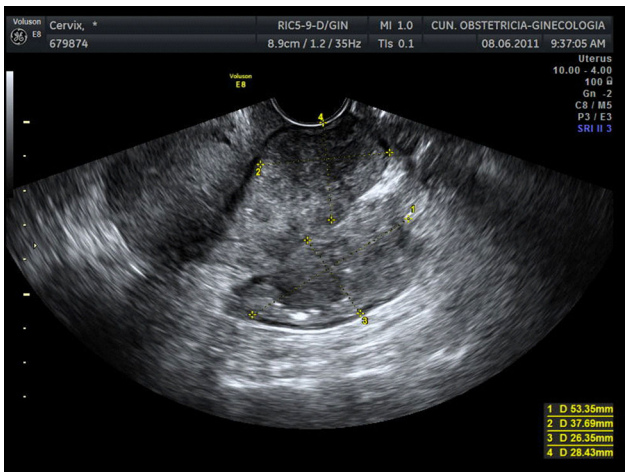

Fig. 6 Transvaginal ultrasound showing a large cervical cancer in longitudinal plane. In this case, rectum involvement is observed

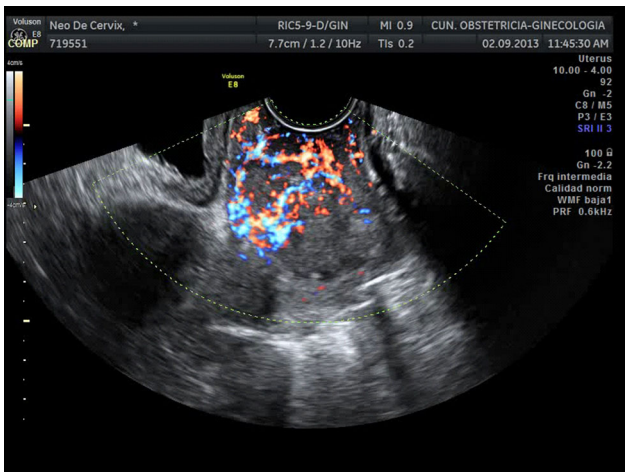

Fig. 8 Transvaginal color Doppler from a cervical cancer showing an abundant vascularization

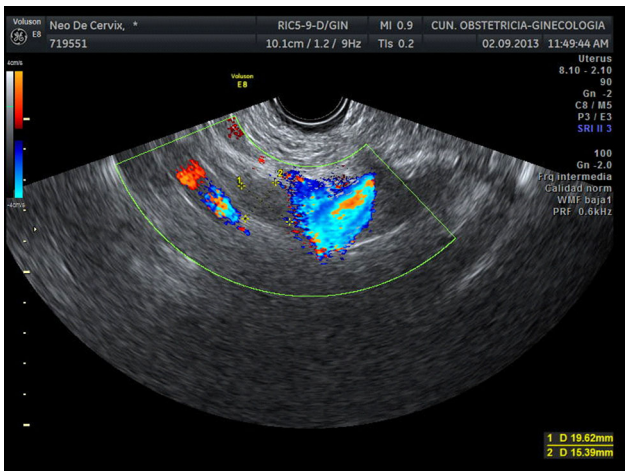

Fig. 7 Transvaginal ultrasound depicting the internal iliac vessels. A suspicious lymph node measuring 19 × 15 mm is observed

is a two-dimensional assessment of tumor vascularity in a given scanning section of the tumor. But the tumor is a three-dimensional structure. Furthermore, this method has not been reproduced by other authors.

The same group reported a further series but using color Doppler in 60 women diagnosed as having a stage Ib-IIa cervical cancer [27]. They found color signals in 58 % of the cases. The presence of color signals was associated with a higher probability of lymph node metastases (sensitivity 80 %, specificity 48 %) and parametrial involvement (sensitivity 91 %, specificity 57 %).

Wu et al. compared color and power Doppler in assessing intratumoral vascularization in 35 women with cervical cancer and 30 healthy women [28]. They reported color signals in 97 % of cancers and found that both PI and a vascular ratio (cross-section area of intratumoral vessels/cross-section area of the tumor) defined by the authors were significantly lower in patients with cervical cancer. They concluded that power Doppler angiography was more useful than color Doppler because the vascular ratio provided more sonographic characteristics among different subclassifications of cervical cancer.

Alcazar et al. reported that color signals could be detected in 100 % of cases of cervical cancer and that tumor blood flow as assessed by transvaginal color Doppler was correlated with some tumor characteristics. Tumor vascularization was higher in squamous cell cancers, moderately or poorly differentiated lesions and advanced-stage tumors [29].

Jurado et al. reported a series of 27 cases of early stage cervical cancer. Their aim was to assess whether intratumoral vascularization as assessed by power Doppler ultrasound could predict those high-risk cases for adjuvant therapy (radiotherapy) after radical surgery [30]. They found that 94 % of high-risk cases the tumor exhibited a high vascularization as compared with 11 % of low risk cases.

However, in all these studies, assessment of tumor blood flow color mapping has the inherent bias of subjectivity and this may represent a problem for inter- and intra-observer reproducibility when applying this technique in clinical setting.

Some reports evaluated the role of three-dimensional power Doppler in cervical cancer with controversial results. Testa et al. did not find any correlation between 3D-derived vascular indices and clinic-pathological characteristics in a series of 74 cervical cancer [31]. However, Hsu et al. has reported the results of applying 3D Power Doppler in 141 patients with early stage cervical cancer.

They found blood flow in 85 % of the tumors and tumor vascularization was correlated with tumor volume [32]. On the other hand, Alcazar et al. [33], Tanaka and Umesaki [34], and Belitsos et al. [35] did find that tumor vascularization as assessed by 3D power ultrasound correlated with some tumor characteristics such as tumor stage and histologic grade.

Notwithstanding caution should be taken since 3D power Doppler ultrasound is not a standardized technique and results might not be reproducible in clinical setting [36].

Ultrasound for Predicting Response to Therapy

Several studies have evaluated the role of transvaginal color Doppler for assessing or predicting the response to treatment in women with cervical cancer.

Pirhonen and col. analyzed intratumoral vascularization by color mapping in 14 patients with advanced cervical carcinoma treated with external radiotherapy [37]. They used a subjective color map grading (from grade 1: normal amount of vessels to grade 5: extremely high amount of vessels). They evaluated patients prior to start treatment and then five follow-up examinations during treatment. These authors found that a decrease in tumor vascularization during radiotherapy was associated with a better outcome, whereas persistence of high vascularity was associated with a poor response. They concluded that color Doppler ultrasound might be useful in early assessment of therapeutic response during RT.

Similar findings were reported by Greco et al. in a series of 14 women with advanced cervical cancer [38]. These authors evaluated intratumoral vascularization by means of transvaginal color Doppler before and after neoadjuvant chemotherapy. Ten out of 14 patients had a successful therapeutic response. The authors reported that in these cases a significant increase on intratumoral RI and PI was observed after treatment, whereas no differences were found in those four women who did not respond to chemotherapy.

More recently, Huang et al. used 3D power Doppler ultrasound for monitoring the response to radiotherapy and to detect tumor recurrence [39]. They found that this technique is useful to assess tumor response during treatment, since responding tumors showed a significant decrease in vascularization, and also it showed a better sensitivity than serum markers to detect recurrence.

Alcazar et al. reported two different studies in which they evaluated the role of transvaginal color Doppler for predicting pathological and clinical response to chemoradiotherapy in locally advanced cervical cancer [40, 41]. They found that poorly vascularized tumors had better response than highly vascularized tumors.

Similar findings have been reported by Chen et al. [42] and Kerimoglu [43].

In conclusion, current evidence suggests that ultrasound may be a useful technique for assessing local extent of disease in cervical cancer, even with higher accuracy than MRI. This technique is limited for assessing lymph nodes. The assessment of tumor vascularization by Doppler ultrasound is controversial. Most reports suggest that it could be useful for monitoring and predicting response to therapy.

Compliance with Ethical Requirements and Conflict of interest IRB approval was obtained. Juan Luis Alcazar, Sara Arribas, and José Ángel Mínguez y Matías Jurado declare that they have no conflict of interest.

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