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Research Article

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Echographic evaluation of uterine cervix cancer before and after chemotherapy

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Abstract

Objective: *To evaluate if echographic and Doppler scans help to access and predict uterine cervix cancer clinical response to chemotherapy.*

Methods: *Using transvaginal ultrasound and Doppler, we scanned 22 uterine cervix epidermöid carcinoma patients, clinical stage II and III before and after three cycles of adjuvant chemotherapy (cisplatin and ifosfamide).*

Results: *Five patients presented complete response (CR), 12 partial response (PR), and five did not respond (NR). Fourteen of the responsive (R) patients were submitted to radical hysterectomy. Before chemo, the main blood inflow was central and abundant in all NR patients. Hydronephrosis was detected by echography after chemo in 3/5 of the NR group while it occurred in one patient in the R group. We found chemotherapy to be effective in reducing uterine and cervix volumes. Chemotherapy induced a significant shrinkage of the uterine cervix in both CR and PR subsets. Although PI and RI did not change under chemotherapy for both R and NR groups, PI and RI from the uterine artery revealed significant differences between CR and PR patients at the time of the initial scan (p=0,01).*

Conclusion: *We found echography an excellent guide tool to follow up tumors of the uterine cervix submitted to chemotherapy.*

Keywords: Uterine Cervix Neoplasm, Adjuvant Chemotherapy, Transvaginal Ultrasound, Doppler.

Ultrasound scan for uterine cervix morphometry is not a standardized method and it does not have universal acceptance neither for the diagnosis of uterine cervix cancer nor population screening. Only bulky tumors of advanced stage, sometimes already accompanied by adjacent structures invasion, as FIGO stage II to IV, are visible to the ultrasound scan. Uterine cervix tumors appear as iso or hypoechogenic images, frequently in irregular and imprecise outlines, deforming shape and/or cervix outline, invading parametric areas, bladder floor, and rectal wall, besides extending to the uterine body or projecting inside the vagina. Echographic patterns of cervix tumors are based on the identification images of distinct echotexture, compared to myometrium. Such images are commonly not well delimited, hypoechogenic, voluminous, extending to surrounding tissues and, sometimes, to internal degenerative areas, suggesting necrosis [1].

Additionally, information about the functionality of organs can be reached by two-dimensional images in real-time, combined with a Doppler beam, which allows analysis of echoes contemplated by moving structures [2]. Due to the neovascularization induced by malignant tumors over 2-3 mm, an increased blood flow can be scanned by Doppler [3].

Evidence of the effectiveness of chemotherapyin advanced uterine cervix cancer is shown in a meta-analysis from Alberts andMasson-Liddil,4 in which the complete response (RC) ratesreached 33% in previously not treated patients submitted to monochemotheapywith cisplatin. It suggested that advanced cancers were responsive and thenconsidered a logical justification for preoperative chemotherapy. In thissituation, drugs are administered before the vascular supply is reduced byeither surgery or radiotherapy [5]. In this work, we aim to determine echographic exam appropriateness

to detect echomorphological changes of the uterus and cervix under cervix malignant tumor, before and after chemotherapy.

1. Patients and Methods

We studied histologically proven uterine cervix epidermoid carcinoma patients, FIGO clinical stage II and III, from the University of Brasília Hospital GYN Oncology clinic, submitted to three cycles of neoadjuvant chemotherapy (cysplatin 75 mg/m^2 and ifosfamide 1 g/m^2) every 21 days.

The transvaginal echographic evaluation was accomplished one day before and four weeks after the completion of chemotherapy. We used a Hitachi ultrasound device, model EUB 555, with a convex transvaginal transductor (5 and 6.5 MHz) equipped with a colored pulse Doppler (Tarrytown, NY). In the study of the uterine cervix, the muscle-collagenous layer adjacent to the myometrium appears as a homogeneous image of intermediary echogenicity. Due to its low muscular fiber content, it can be slightly less echogenic than the myometrium. The adventitia appears as a hyperechogenic contour outlining the cervix.

The components of the cervical stroma and glandular epithelium generate echoes that change during the whole menstrual cycle. The endocervix is more evident than the myometrium, appearing as an echogenic line, usually virtual, but that can be distended by a hypoechoïc image, usually corresponding to mucus, during the peri-ovulatory phase. It is easy to identify anterior and posterior cervix lips using the external os as a reference. For this study, the cervix longitudinal extension was defined as the distance between the internal and external os (Figure 1)

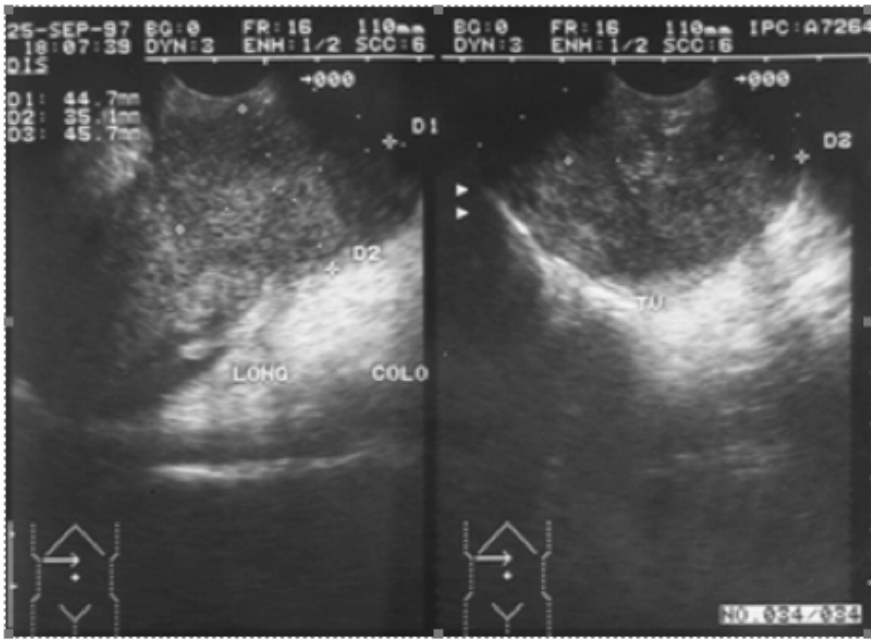

Figure 1: Echographic measurement of the uterine cervix. The uterus and the cervix were evaluated in their longitudinal (right) and coronal axis (left). We measured the three largest diameters of the cervix.

The patient was placed in a dorsolithotomy position; with the bladder partially full. The uterus and the cervix were evaluated in their longitudinal and coronal axis. We measured the three largest diameters of the cervix and the longitudinal, anterior-posterior, and transverse diameters of the uterus. Each volume was calculated from the multiplication among the measurements of the three diameters. The result was multiplied by 0.52.

A Dopplerfluxometric scan of the uterine arteries and tumor arteries (when present) was also accomplished, by the analysis of the profile of the wave speed and measurement of the pulsatility index (PI) and resistance index (RI). We made two measurements for each index and calculated the average. The PI can be defined by the formula: maximum systolic speed *minus* telediastolic speed, divided by the medium speed [6]. The Resistance Index (RI) is the maximum systolic speed minus telediastolic speed, divided by systolic speed (Figure 2) [7].

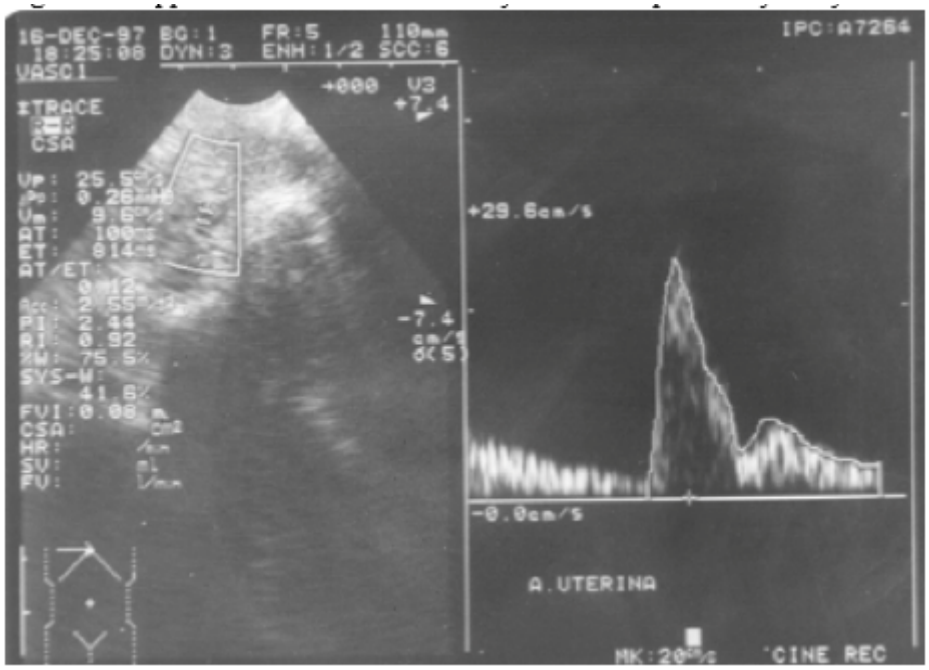

Figure 2: Doppler scan of the uterine artery was accomplished by analysis of the profile of the wave speed and measurement of the pulsatility index (PI) and resistance index (RI).

The evaluation of the intratumor vascular pattern was made verifying the main distribution of blood flow in the tumor, whether central or peripheral. We also quantified the flow into absent, discreet (less than 2/3 of the screen image has identifiable flow), or abundant (2/3 or more of the screen image present flow) (Figure 3).

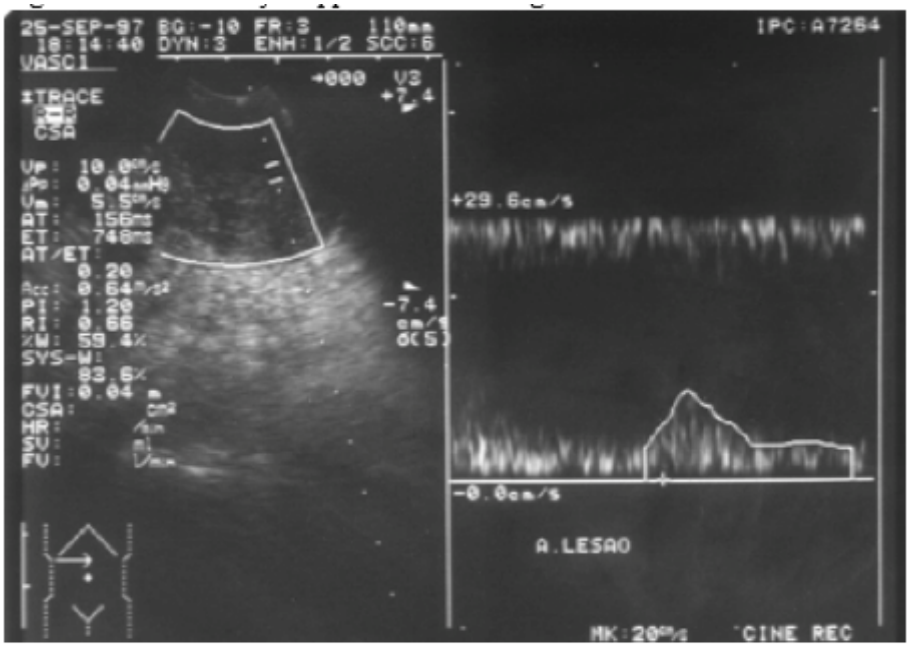

Figure 3: Tumor artery Doppler scan showing central and abundant flow.

Measuring the distance from the tumor to the bladder or observing hydronephrosis accomplished the evaluation of the presence of urinary tract lesions.

We submitted all patients to an echographic study before chemotherapy, and retrospectively we classified patients into two groups: responsive (R) and non-responsive (NR), according to the tumor behavior under the chemotherapic regimen. The R group was also sub-grouped into complete response (CR) or partial response (PR). As for statistics we compared two groups by T test and correlated several groups by Mann and Whitney test [8].

All patients signed informed consent, previously approved by the University's IRB.

2. Results

From March 1996 to October 1997, we admitted 22 patients, aged from 29 to 57 years (mean 40.8). One patient was stage IIA, thirteen were stage IIB, and eight patients were stage IIIB. The responses to chemotherapy were 1/1 in stage IIA; 11/13 for stage IIB and 5/8 for stage IIIB, there was a progressive tendency to decrease in the responses with the increase of the stage, although not statistically significant (p=0.47, Fisher's Test). Five patients presented histology-proven complete response (CR), 12 partial responses (PR), and five did not respond (NR). The total number of patients who responded was 17 (77,3%). Fourteen of the responsive (R) patients were submitted to radical hysterectomy with or without lymphadenectomy. Five showed no residual tumor (CR). Nine patients had residual tumors measuring an average of 2.8 cm in their largest diameters. One patient presented with a vaginal margin tumor. All patients' parameters were histologically considered free from disease.

We were unable by echography to identify the cervix tumor in a patient in the R group, before chemotherapy. This event was more common after chemotherapy, as we did not see any tumors in 10 patients.

Before chemo, the main blood inflow was central and abundant in all NR patients. R tumors tended to yield abundant and central flow in only 9/17 and 8/17 respectively. After chemotherapy, the flow was abundant and central in 4/5 NR patients (one discrete flow), while it could be seen in only 2/17 in the R group, and only one patient showed central flow.

Before chemotherapy, hydronephrosis was detected by echography in 5/17 in the R group and 2/5 in the NR group. After chemo, hydronephrosis persisted or appeared in 3/5 of the NR group while it occurred in one patient in the R group.

By ultrasound measurements, the mean uterine volume for the R group was 94 cm^3 (26 to 259), and 122 cm^3 (30 to 188) for the NR group. Of more interest, the mean uterine cervix volume was 25 cm^3 (4 to 69) for the R group and 47 cm^3 (8 to 117) for the NR group. We found chemotherapy to be effective in reducing uterine and cervix volumes (Table 1).

Mean Volume (cm^3)	Before Chemotherapy	After Chemotherapy	*p*
Uterus	100.11	64.57	0.001
Cervix	29.67	13.18	0.0012

Table 1: Mean uterine and uterine cervix volumes measured before and after chemotherapy.

However, the shrinkage was larger and significant only for R patients (Table 2).

Uterine Volume Before Chemotherapy	Group	Uterine Volume After Chemotherapy	*P*
93.56 cm^3	R	58.65 cm^3	0.02
122.36 cm^3	NR	84.71 cm^3	Ns
Cervix Volume Before Chemotherapy		**Cervix Volume After Chemotherapy**	
24.75 cm^3	R	6.47 cm^3	0.004
46.41 cm^3	NR	36.01 cm^3	Ns
Ns is non-significant.			

Table 2: Mean uterine and uterine cervix volumes, before and after chemotherapy compared to response.

PI and RI, either the uterine or tumor artery, did not change under chemotherapy for both R and NR groups (Table 3).

PI Before Chemotherapy	Group	PI After Chemotherapy	*p*
2.06	R	2.29	Ns
1.65	NR	1.84	Ns
RI Before Chemotherapy		**RI After Chemotherapy**	
0.82	R	0.86	Ns
0.78	NR	0.77	Ns
Ns is non-significant.			

Table 3: Mean uterine artery Doppler Pulsality and Resistance Index before and after chemotherapy compared to response.

Statistical analysis correlating parameters of echo graphic evaluation pre-chemotherapy (uterine volume, cervix volume, PI, and RI of uterine and tumor arteries) to the therapeutic response was not significant (Mann-Whitney).

In the R group, 14 patients were submitted to radical hysterectomy. From these patients, we found five histologically proven complete responses and nine partial responses. We studied the echo graphic features probably involved with the complete or partial response. Chemotherapy induced a significant shrinkage of the uterine cervix in both CR and PR subsets. The uterine volume also became smaller, but the shrinkage was not significant.

Uterine Volume Before Chemotherapy	**Group**	**Uterine Volume After Chemotherapy**	***p***
80.4 cm^3	CR	51.6 cm^3	Ns
104.3 cm=	PR	66.2 cm^3	Ns
Cervix Volume Before Chemotherapy		**Cervix Volume After Chemotherapy**	
17 cm^3	CR	6.4 cm^3	0.02
28.4 cm^3	NR	6.3 cm^3	0.003
Ns is non-significant.			

Table 4: Mean uterine and uterine cervix volumes, before and after chemotherapy in responsive patients, compared to intensity of response.

(Table 4) On the other hand, we were unable to foresee a complete response comparing CR to PR for uterine and cervix volume. We did not find a significant difference between these two subgroups at the time of the initial scan.

PI Before Chemotherapy	**Group**	**PI After Chemotherapy**	***p***
1.62	CR	0,758	0,04
2.42	PR	2.27	Ns
RI Before Chemotherapy		**RI After Chemotherapy**	
0,76	CR	0,86	0,04
0,86	PR	0,88	Ns
Ns is non-significant.			

Table 5: Mean uterine artery Doppler Pulsality and Resistance Index before and after chemotherapy compared to response.

The PI and RI Doppler measurements at the tumor artery did not differ for CR or PR either. On the other hand, the PI and RI from the uterine artery revealed significant differences between CR and PR patients (Table 5). Both PI and RI were significantly different when comparing CR and PR at the time of the initial scan. (p=0,01 and p=0,01, respectively).

3. Conclusion

We found a transvaginal ultrasound scan effective to evaluate objective response to uterine cervix cancer chemotherapy. Uterine cervix morphometric measurements before and after treatment were consistent with response to chemotherapy, although we were unable to foresee treatment's response or failure based on uterine or cervix measurements. The central and abundant flow seemed to be related to a worse prognosis, especially when we found tumor blood flow after treatment. Hydronephrosis found after chemo appears to be a strong marker of treatment failure. Although PI and RI from either the uterine or tumor artery did not change under chemotherapy for both R and NR groups, the PI and RI from the uterine artery revealed significant differences between CR and PR patients, a promising sign of a possible response predictor based on Doppler. Both PI and RI were significantly different compared to CR and PR at the time of the initial scan (p=0,01 and p=0,01, respectively). It may suggest more responsive tumors tend to have an increased flow compared to PR tumors before treatment. Ultrasound proved to be useful in our settings. It provided objective tumor measurements, helped to trail the tumor's behavior, and was both safe and reliable. We believe the history of ultrasound and uterine cervix cancer staging and control still waits to be written.

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