Transvaginal colour Doppler ultrasound in predicting response to chemoradiation in patients with carcinoma of the cervix

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Abstract

Background: The objective of the study was to evaluate the potential role of transvaginal colour Doppler ultrasound (TVCDUS) in predicting response to chemoradiotherapy in patients with locally advanced cervical cancer.

Method: TVCDUS was used in 56 patients with histologically proven cervical carcinoma (stage IIA–IIIB) before the start of chemoradiation, and after one and three months of therapy. Resistive index (RI) and pulsatality index (PI) were calculated using TVCDUS. Tumour response to chemotherapy was determined. Complete response was when no residual tumour was found, partial response if the tumour volume decreased by more than 50%, and no response when there was no appreciable change in the size of tumour, or the tumour volume decreased to less than 50% of the original volume.

Results: A statistically significant increase in RI and PI was demonstrated with TVCDUS following treatment in patients who had a complete and partial response to chemoradiation, compared to those who had no response.

Conclusion: TVCDUS is useful in predicting clinical response to concurrent chemoradiation in patients with locally advanced cervical cancer. Thus, it is recommended during the pretreatment evaluation and follow-up.

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Introduction

Cervical cancer is the most common genital tract malignancy affecting women. It is the fourth most common cancer in women after breast, and colorectal and lung cancer. Seventy per cent of new cases are diagnosed in developing countries. India alone accounts for one fifth of the total.[1] It remains a disease of significant morbidity and mortality, causing 5% of all cancer deaths.[2]

The treatment of cervical cancer depends upon the stage and grade of malignancy. Treatment options for carcinoma in situ include laser therapy, cryotherapy, conisation and electrosurgical excision. Surgery is required for the early stages of invasive cervical cancer, i.e. International Federation of Gynecology and Obstetrics (FIGO) stage 1A–IIB. Chemoradiotherapy is currently the standard of care for locally advanced disease, i.e. FIGO stage IIB–IVA.[3,4]

Radiation therapy starts with an initial course of radiation by external beam to reduce the tumour mass to enable subsequent intracavitary application. Brachytherapy is delivered using afterloading applicators placed in the uterine cavity and vagina.

Chemotherapy may act synergistically with radiotherapy. Cisplatin is the most widely used drug for carcinoma of the cervix chemotherapy. It damages cellular DNA, inducing apoptosis and preventing the repair of radiation-induced damage.

Angiogenesis is essential for tumour growth, and correlates with tumour metastatic potential.[5] Several studies have demonstrated that it is an independent prognostic factor.[5-7] Tumour vascularity in cervical cancer can be assessed in vivo by transvaginal colour Doppler ultrasound (TVCDUS). Alcazar and Jurado[8] assessed tumour vascularity by TVCDUS, and found that less vascular tumours had a greater response to chemoradiotherapy.

The present study was aimed at assessing TVCDUS as a means of predicting the clinical response to concurrent chemoradiation in locally advanced cervical carcinoma.

Method

Fifty-six patients with histologically proven locally advanced carcinoma of the cervix (stage IIA–IIIB) were included in this study. Informed written consent was obtained from each patient. A brief patient history was taken, and a clinical examination conducted, including a per vaginal examination, together with routine blood investigations, including a kidney and liver function test, to assess the suitability of the patient for chemoradiation.

Staging of cervical carcinoma was carried out on the basis of the FIGO staging system by examining the spread of lesion on the basis of a clinical pelvic examination and magnetic resonance imaging (MRI).

Chemoradiation given was cisplatin (40 mg/m^2) to sensitise the cells, a 25 fractions of teletherapy and two brachytherapy schedules to make a total of 8 000 cGy to point A (2 cm superior to the external os and 2 cm lateral to the internal uterine canal), and 6 000 cGy to point B (3 cm lateral to point A).

Tumour vascularity was assessed by TVCDUS with a 5-8 MHz transvaginal transducer before the start of concurrent chemoradiotherapy, and at one and three months after completion of the treatment. With the patient in the lithotomy position, the ultrasound probe focused on the cervix, and a clear view was obtained of the ascending uterine artery in the parasaggital plane. The cervix was thoroughly examined and Doppler signals recorded from within the wall and around the cervical canal. Resistive index (RI) and pulsatality index (PI) were measured from the uterine vessels on both sides for each case.

Patients were clinically evaluated per vaginal examination, TVCDUS and MRI after completing the chemoradiation schedule.

Clinical response was judged as:

- A complete clinical response when no residual tumour was found.
- A partial clinical response when the tumour volume decreased by more than 50%.
- No clinical response, when there was no appreciable change in the size of tumour, or the tumour volume decreased by less than 50%.

Statistics

All the data were analysed statistically using XLSTAT® Statistics calculator software. The difference in the mean value of any two groups was analysed using the *t*- test, and by analysis of variance in the case of more than two groups. The Mann-Whitney U test was used to compare continuous data. A *p*-value of < 0.05 was considered to be statistically significant.

Results

A complete response was reported in 58% of the patients, a partial response in 32% and no response in 10%. The clinical response was not affected by the size of tumour, but related to the stage of disease and histopathology of the tumour. Well-differentiated and moderately differentiated tumours responded best. There was not much variation between the different histopathologies of squamous cell cervical carcinoma, with respect to the mean RI and PI. However, the mean adenocarcinoma RI and PI was significantly lower.

A significant increase was seen in both the RI and PI of patients with a complete response. The increase in patients with a partial response was less significant, whereas there was no change in the RI and PI of patients with no response. Tumours which subsequently responded completely had a significantly higher pretreatment RI and PI than those with no response or a partial response. The TVCDUS of one patient each with subsequent complete response, partial response and no response has been shown in Figures 3-5. In patients who ultimately showed a complete response, the mean pretreatment RI ranged from 0.73 ± 0.21, whereas that in patients with a partial response varied from 0.66 ± 0.15, and from 0.64 ± 0.05 in patients with no response. Similar values for PI were 1.39 ± 0.65 in patients with a complete response, 1.14 ± 0.47 in those with a partial response, and 1.10 ± 0.00 in patients with no response (Tables 1 and 2). Three months after treatment, the corresponding RI values were 1.50 ± 0.85 for a complete response, 1.09 ± 0.41 for a partial response, and 0.62 ± 0.10 for no response. Similarly, the PI values were 2.27 ± 1.10 for a complete response, 1.99 ± 0.99 for a partial response and 1.16 ± 0.12 for no response.

Table 1: Mean ± standard deviation of the resistive index at pre-chemoradiotherapy, and at one and three months according to clinical response

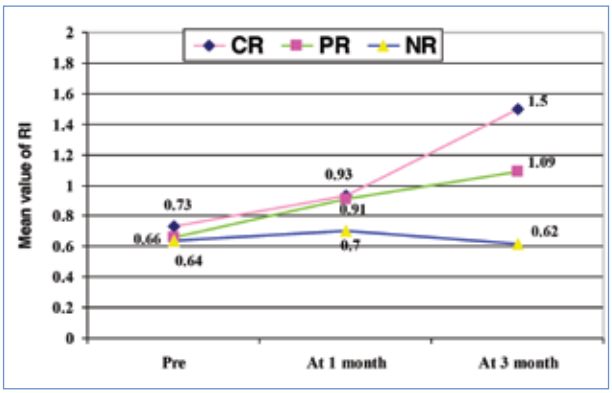
Clinical response	Mean ± SD			Mean change ± SD (0–3 months)	*p*-value	Significance
	Pre-chemoradiotherapy	1 month	3 months			
Complete response	0.73 ± 0.21	0.93 ± 0.64	1.50 ± 0.85	0.77 ± 0.81	< .001	Highly significant
Partial response	0.66 ± 0.15	0.91 ± 0.41	1.09 ± 0.41	0.43 ± 0.45	< .001	Significant
No response	0.64 ± 0.05	0.70 ± 0.00	0.62 ± 0.10	0.02 ± 0.15	> .050	Not significant

SD: standard deviation

Table 2: Mean ± standard deviation of pulsatality index at pre-chemoradiotherapy, and at one and three months according to clinical response

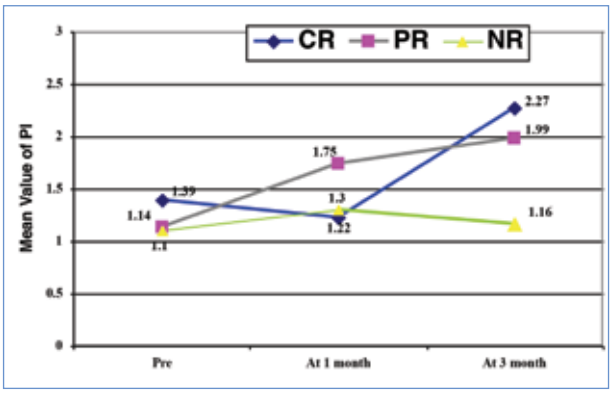
Clinical response	Mean ± SD			Mean change ± SD (0–3 months)	*p*-value	Significance
	Pre-chemoradiotherapy	1 month	3 months			
Complete response	1.39 ± 0.65	1.22 ± 0.85	2.27 ± 1.10	0.87 ± 1.05	< 0.001	Highly significant
Partial response	1.14 ± 0.47	1.75 ± 0.63	1.99 ± 0.99	0.85 ± 0.96	< 0.001	Significant
No response	1.10 ± 0.00	1.30 ± 0.25	1.16 ± 0.12	0.06 ± 0.12	> 0.050	Not significant

SD: standard deviation



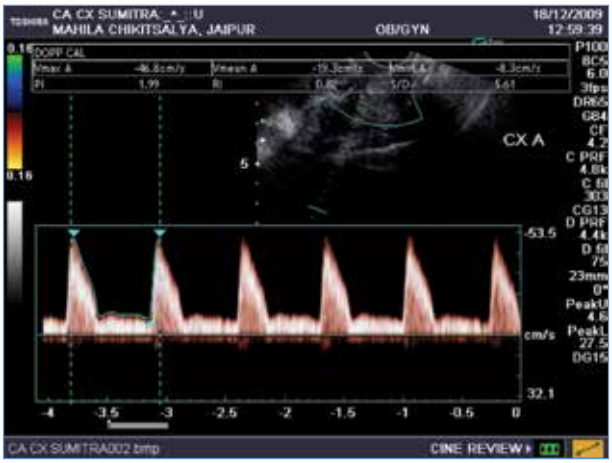
CR: complete response, NR: no response, PR: partial response, RI: resistive index

Figure 1: Mean ± standard deviation of resistive index at pre-chemoradiotherapy, and at one and three months according to clinical response



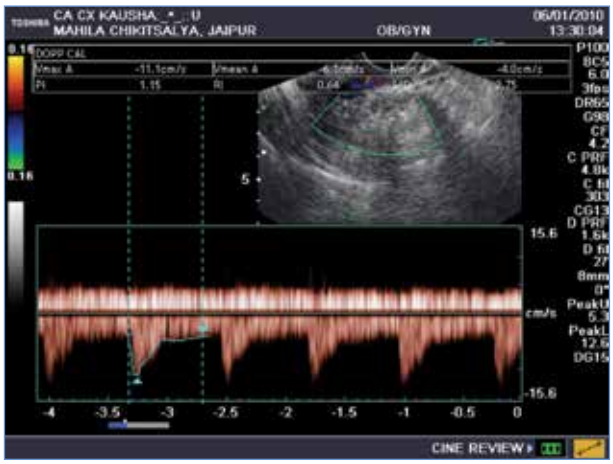
CR: complete response, NR: no response, PI: pulsatality index, PR: partial response

Figure 2: Mean ± standard deviation of pulsatality index at pre-chemoradiotherapy, and at one and three months according to clinical response



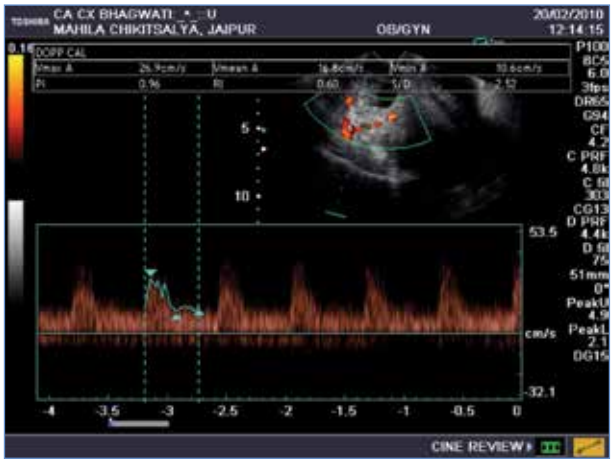
Note the high resistive index and pulsatality index

Figure 3: A transvaginal colour Doppler ultrasound of cervical cancer with subsequent complete response



Note the resistive index of 0.64 and pulsatality index of 1.15

Figure 4: A transvaginal colour Doppler ultrasound of a tumour with subsequent partial response



Note the low resistive index of 0.60 and pulsatality index of 0.96, as well as abundant vascularity

Figure 5: A transvaginal colour Doppler ultrasound of a tumour with subsequent no response

Discussion

Tumour vascularity is an important factor for growth and metastasis in carcinoma of the cervix. Previously, many studies have demonstrated that highly vascular tumours are more malignant and therefore have poorer prognosis.[6,7] Neovascularistion is an important prognostic factor in cervical carcinoma, and is also a predictor of recurrence.[9,10] It has been observed that chemotherapy has more of an impact on cervical cancer that has less microvessel density.[11]

The use of TVCDUS in earlier studies focused mainly on the main blood vessels that feed the cervix, i.e. the uterine artery and the cervical branch of the uterine artery. Hata et al[12] studied transvaginal colour TVCDUS in reproductive tract tumours and found that the RI was considerably lower in cervical, endometrial and ovarian carcinoma, compared to that in normal subjects. Further studies found the PI to be lower in patients with cervical carcinoma.[13,14]

Our study used TVCDUS to assess response to chemoradiation in locally invasive cervical carcinoma, and found that both the RI and PI correlated directly with the response. A similar study by Greco et al[15] evaluated tumour vascularisation by means of TVCDUS in patients with carcinoma of the cervix prior to and after neoadjuvant chemotherapy. Of the 14 patients, there was a significant increase in RI and PI in the 10 who responded to chemotherapy. Differences were not found in the other four patients who did not respond to chemotherapy.

Cheng et al[16] also assessed tumour angiogenesis by TVCDUS and found that the microvascular density detected by TVCDUS and immunohistochemistry correlated well. In another study, Cheng et al[17] found that the colour signals detected by TVCDUS were associated with a higher incidence of parametrial invasion and lymph node metastasis.

Tumour vascularity was found to be much more significant than even lymph node status in determining the survival of patients with cancer of the cervix in some studies.[18] Interestingly, it was found that patients with positive lymph nodes and low tumour vascularity had a better prognosis than those with negative lymph nodes and high tumour vascularity. Therefore, tumour vascularity may be as significant a determinant of outcome as lymph node status, or even more so.

Thus, the assessment of tumour vasculature by TVCDUS can be a cost-effective alternative to MRI in predicting the response of cervical carcinoma to chemoradiation. This is particularly important in developing countries, like ours, where costly imaging modalities, such as MRI, are not easily available and are also are beyond the reach of many patients.

However, owing to the small number of patients in this study, it is not possible to comment on the extent of the effectiveness of this technique, especially in patients who only obtained a partial response. Therefore, further studies in which there is a greater number of patients are required before any definite recommendation can be made.

Conclusion

TVCDUS can be useful in predicting clinical response to chemoradiation in locally advanced cervical cancer. Thus, it is recommended in the pretreatment evaluation and follow-up of such patients.

Conflict of interest: The authors have no commercial or other affiliation which might have caused a conflict of interest when conducting this study.

Declaration: Financial support was not obtained for this study.

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