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Acute toxicity profile of three-dimensional conformal concurrent chemoradiation in carcinoma cervix: an institutional experience

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Original Article

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Abstract

Background: Concurrent chemoradiation is the definitive treatment for advanced cervical cancer. Pelvic radiation is known to damage the adjacent normal tissues thereby causing acute toxicities. The modern conformal radiation techniques like three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy are known to reduce the toxicities and improve clinical outcomes.

Aim: To retrospectively evaluate the frequency and severity of acute toxicities encountered during concurrent chemoradiation of locally advanced cancer cervix treated with 3D-CRT.

Methods: The medical case records of 174 cervical cancer patients treated between November 2015 and November 2018 were studied. One hundred and thirteen histologically proven locally advanced cancer cervix patients (Stage IIB–IIIB) treated with concurrent 3D conformal chemoradiation between were included in the study. Patients received 46 Gy in 23 fractions with concurrent weekly cisplatin (40 mg/m^2) on days 1, 8, 15 and 22 of radiation. The study endpoints were treatment-related toxicities which were graded according to CTCAE version 5.0.

Results: One hundred and thirteen patients were analysed for the study. Gastrointestinal toxicity was the predominant toxicity observed followed by haematological toxicity. 31·7% patients reported grade 1–2 diarrhoea and 39·7% reported grade 1–2 leucopenia. None of the patients reported grade 3 or higher toxicities. Treatment interruptions were noted due to these toxicities.

Conclusion: Concurrent chemoradiation is the definitive treatment for locally advanced carcinoma cervix with acceptable toxicities. Proper management measures should be undertaken for these toxicities to avoid treatment interruptions and ensure better treatment compliance.

Introduction

Cervical cancer is the fourth most common cancer of women worldwide in terms of incidence and mortality.[1] Pelvic radiation is an integral part of definitive management of gynaecologic malignancies. Traditionally, two-dimensional radiotherapy (2D-RT), using bony anatomy to localise treatment, was employed for pelvic irradiation, resulted in unnecessary irradiation of normal tissues causing acute haematological, genitourinary (GU) and gastrointestinal (GI) toxicities. Radiotherapy has evolved gradually with the advent of modern techniques of image-guided radiotherapy in the form of three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). Image-guided radiotherapy allows better target coverage and normal tissue sparing.[2] Despite the modern conformal techniques employed for pelvic irradiation, the adjacent normal tissues do get damaged, resulting in treatment-related toxicity affecting treatment compliance. GI and haematological toxicities are commonly encountered during concurrent chemoradiation of cervix.

IMRT is known to deliver precise high doses to target area and minimise the radiation dose to the adjacent normal tissues, thereby resulting in reduced normal tissue toxicities. IMRT is still not routinely recommended for the treatment of locally advanced cervical cancer. It has been reported that IMRT was not superior to 3D-CRT or 2D-RT in terms of overall survival (OS), but it was associated with relatively few instances of acute GU and (GI toxicities.[3] 3D-CRT is known for better tumour coverage and reduced GI toxicity as compared to 2D-RT.[4] 3D-CRT serves to be a good radiotherapy technique for pelvic radiation in centres with high numbers of patient throughput.

Five randomised Phase III clinical studies[5–9] and two meta-analyses[10,11] showed significant improvement in OS and progression-free survival with radio-chemo-concurrence with platinum, when compared to radiotherapy alone, or with radiotherapy and hydroxyurea, thereby making concurrent chemoradiation as the standard treatment for locally advanced cervical cancer.

Our institute is the only government centre for radiation treatment in our state catering to the needs of its own population along with a subset of population from the neighbouring states.

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Hence, due to high patient throughput, the institute employs 3D-CRT technique to treat cervical cancer.

In order to better understand the outcomes of this treatment technique on our patients, the aim of this study was to evaluate the acute toxicity profile in cervical cancer patients who underwent concurrent chemoradiation in our tertiary care centre.

Materials and Methods

After gaining ethical approval from our institute, we undertook a retrospective analysis of the medical case records of 174 cervical cancer patients treated between November 2015 and November 2018. One hundred and thirteen histologically proven locally advanced cancer cervix patients (Stage IIB–IIIB) treated with concurrent 3D conformal chemoradiation between were included in the study. Patients received 46 Gy in 23 fractions with concurrent weekly cisplatin (40 mg/m^2) on days 1, 8, 15 and 22 of radiation.

Patients selected for the study were histologically proven cases of squamous cell carcinoma cervix. Patients staged with International Federation of Obstetrics and Gynecology[12] Stage IIB–IVA with Eastern Cooperative Oncology Group (ECOG)[13] performance status 0–2 were included in the study.

Radiation technique

Simulation

Virtual simulation in supine position with full bladder was performed using CT scan with a section thickness of 5 mm. The CT scan was obtained from L2 vertebral body to the lower edge of ischial tuberosity. Images were then transferred to Monaco treatment planning system (Elekta, Crawley, UK) workstation for analysis.

Contouring and treatment planning

The target volumes and organs at risk were delineated following Radiotherapy Oncology Group guidelines.[14,15] Gross visible tumour and its visible extension were contoured as gross tumour volume (GTV). Whole GTV, uterine cervix, uterine corpus, parametrium and vagina were contoured as clinical target volume (CTV). The relevant draining nodal groups included common internal and external iliac (with abdominal aortic bifurcation as CTV superior margin), obturator and presacral lymph nodes. A margin of approximately 1–1·5 cm around the CTV in the region of uterus and cervix and 0·7 mm in the nodal CTV regions were given for planning target volume to account for uterine motion and set-up errors.[4] Normal tissues contoured included bowel, bladder and rectum. 3D-CRT planning was done using Xio treatment planning system (Elekta, Atlanta, GA, USA). Dose prescription for pelvic external beam radiotherapy (EBRT) was set at 46 Gy/23#.

- Chemotherapy: Patients were administered cisplatin (40 mg/m^2) weekly concurrently on days 1, 8, 15 and 22 of radiation.
- Toxicity evaluation: Patients were assessed weekly by the radiation oncologist throughout the treatment for acute toxicities in accordance with CTCAE version 5.0.[16] Complete blood counts and renal function tests were performed weekly prior to chemotherapy.

Results

One hundred and thirteen patients treated with 3D-CRT between November 2015 and November 2018 were analysed. The patient, tumour and treatment characteristics are presented in Table 1. The median age of the patients was 50 years. Eighty percentage of the patients had ECOG performance status 1 while 20% had performance status 2.

GI toxicity was the most common toxicity observed in our treatment population. These patients developed GI toxicity in the form of nausea, vomiting and diarrhoea. Nausea was seen as the most frequent GI toxicity observed in all of the patients (Table 2).

Table 1. Pre-treatment characteristics

Characteristics	Number	Percentage
Age		
20–40 years	22	19·46
40–60 years	75	66·37
>60 years	16	14·15
Histology		
WDSCC	43	38·05
MDSCC	44	38·93
PDSCC	19	16·81
ADENOCA	4	3·53
Small cell CA	3	2·65
Stage		
IIB	41	36·28
IIIA	07	6·19
IIIB	59	52·21
IVA	06	5·30
Duration of RT		
<5 weeks	70	61·94
>5 weeks	43	38·05
Concurrent CT		
1–3 cycles	31	27·43
4 cycles	82	72·56
Performance status		
ECOG 1	90	79·64
ECOG 2	23	20·35

Abbreviations: WDSCC, Well differentiated squamous cell carcinoma; MDSCC, Moderately differentiated squamous cell carcinoma; PDSCC, Poorly differentiated squamous cell carcinoma; ADENOCA, Adenocarcinoma.

Table 2. Treatment toxicity

Toxicity	Grade 0	Grade 1	Grade 2
Gastrointestinal			
Nausea	82	28 (24·7%)	3 (2·6%)
Vomiting	79	30 (26·5%)	4 (3·5%)
Diarrhoea	77	27 (23·8%)	9 (7·9%)
Haematological			
Anaemia	93	15 (13·2%)	5 (4·4%)
Leucopenia	68	38 (33·6%)	7 (6·1%)

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Overall 49·5% of patients developed haematological toxicity of some grade in our study. Twenty-nine patients developed grade 1 anaemia. Thirty eight (33·6%) patients developed grade 1 leucopenia during the treatment.

Acute toxicities led to treatment interruptions in 43 (38·05%) patients, who completed their radiation treatment in 6–7 weeks instead of the scheduled 5 weeks. These patients were given supportive care and radiation was continued with gap correction. Due to treatment toxicities, only 72% of the patients completed all four cycles of concurrent chemotherapy. All the patients completed the scheduled dose of EBRT.

Discussion

Concurrent chemoradiation is the standard of care in cervical cancer. Conformal radiation aims to escalate dose to target volume, while minimising dose to normal tissues and reducing local tissue toxicity.[2] We analysed the frequency and severity of acute toxicities encountered during concurrent chemoradiation in our study.

Acute GI toxicity was seen as the predominant toxicity in our study. Although, the frequency of GI toxicity was lower in comparison to other studies. None of our patients reported grade 3 toxicity. Keys et al. reported high rates of toxicities in the range of 18–31% grade 1 and 15–31% grade 2.[4,5,8] Our patients tolerated treatment well in comparison to these studies and had lower rates of treatment toxicities.

Diarrhoea was seen to be predominant in our study followed by vomiting. Grade 1 diarrhoea was noted in 24·7% of patients and grade 2 was seen in 2·6% of patients. Symptomatic management is of utmost importance for ensuring better treatment compliance. The patients were prescribed analgesics for pain in abdomen and anti-diarrhoeal medications along with oral rehydration solution. The patients were administered intravenous fluids to correct dehydration. The toxicities of even a minor grade impacted the quality of life of our patients, discouraging them towards continuing on with the radiotherapy. The patients were regularly counselled and motivated during the entire duration of radiation treatment.

Dracham et al. had reported clinical outcomes using 3D-CRT and had reported grade 1 or 2 acute toxicities in their study population. Acute grade ≥3 skin, vomiting and lower GI toxicity were observed in 3 (1·4%), 11 (5·2%) and 12 (5·7%) patients, respectively. Grade 1 and grade 2 haematological toxicity was seen in 113 (53·8%) and 41(19·5%) patients, respectively. Only 3 (1·4%) patients had grade 3 haematological toxicity.[17]

Haematological toxicity was the second most common toxicity reported in our study. Our study reported 39·7% incidence of grade 1–2 leucopenia which was lower in comparison to the study of Dracham et al. Anaemia was also noted in our study. Five patients had grade 2 anaemia requiring blood transfusion. Blood transfusion caused treatment interruptions of 2–3 days in radiotherapy. Leucopenia was managed with administration of injection of granulocyte colony-stimulating factor subcutaneously given on outpatient basis, and hence there were no treatment interruptions.

Radiotherapy along with radio-sensitising chemotherapy has improved the local control and OS in comparison with radiotherapy alone, but it has also increased the treatment-related toxicity.[4] Addition of concurrent cisplatin led to the increase in myelosuppression, thereby causing decrease in the number of patients who could complete all four cycles of chemotherapy. Only 74% of patients completed all four cycles of chemotherapy.

The non-availability of a brachytherapy machine at our institute caused prolongation of total treatment time as the patients had to be referred to other centres. This led to a decrease in treatment compliance as some patients did not attend for brachytherapy due to the long distance between treatment centre and their residing place, lack of awareness of the importance of attending brachytherapy centre and even due to financial constraints.

Age is an important predictor of acute radiation-induced morbidity. Laurentius et al. found worse tolerance of concurrent chemoradiation in elderly patients.[18] Our study showed similar trends of toxicity in women aged >55 years.

The limitations of our study were that this is a single institutional experience and the results may differ with other centres. The second limitation of this study was that it was retrospective, and hence some case records may have had incomplete information.

Conclusion

Acute toxicities are commonly encountered during concurrent chemoradiation of cervix which should be properly managed to ensure better treatment compliance. 3D-CRT technique serves to be a feasible and acceptable treatment for cervical cancer patients in institutes with a high patient load.

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Conflicts of Interest. None.

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