Volume Based Pulsed-Dose-Rate Brachytherapy Boosting Concurrent Chemoradiation as a Definitive Treatment Modality in Cervical Cancer

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OBJECTIVE

To report the treatment outcomes and treatment induced adverse events (AEs) of concomitant chemoradiation therapy (CRT) boosted with pulsed-dose-rate (PDR) brachytherapy utilizing volume based two-dimensional planning in patients with cervical cancer.

MATERIALS AND METHODS

Patient selection: This is a retrospective study that was approved by the institutional review board. Charts of patients with stages IB to IIB squamous cell carcinoma (SCC) of the cervix treated between January 2006 and December 2008 and assigned to receive definitive CRT in the form of external beam radiation therapy (EBRT) concurrent with weekly cisplatin chemotherapy followed by PDR BT at our institution.

Concurrent Chemoradiation: All patients received EBRT to a total dose of 45 Gy, 1.8 Gy/fraction, 5 fractions per week for a total of 5 weeks. Patients with histopathologically confirmed positive para-aortic lymph nodes received 45 Gy to the para-aortic region. Involved lateral parametrium and/or macroscopic involved pelvic nodes were boosted with three-dimensional fields that encompassed known areas of disease to achieve a total dose of 60 Gy. Parametral three-dimensional boost was individualized based on the extension and volume of gross parametrial disease and tumor topography. Whenever the parametrical extension could be included within the BT isodose line, no EBRT parametral boost was prescribed. All patients received weekly cisplatin chemotherapy concurrent with Radiation 5 weeks with dose 40mg/m2.

Brachytherapy: All patients had examination under anesthesia and radiological evaluation after EBRT and before starting their scheduled BT. The TV was defined in each patient based on the initial tumor volume and the residual disease after EBRT. An envelope that encompassed the TV was drawn on a 2D film and every effort was done to optimize the BT dose to this envelope. On an anterior pelvis x-rays film, we reported the 20 Gy BT isodose line to the corresponding imaged target and this isodose line was matched to the inner border of the parametral boost.

The volume of an isodose cut of 60 Gy as well as the dose to the envelope, the maximum and mean doses to rectum and bladder, and the dosis to the pelvic lymph nodes were all reported. The mean rectal and bladder volumes were defined as the mean of the different volumes recorded in 2D. In this study, we reported: the envelope doses, the maximum and mean doses to rectum and bladder and the volume encompassed by the isodose cut of 60 Gy. BT planning was based on the 2D orthogonal X-rays film, the catheter reconstructions were performed on the 3D X-rays film, and the planning system and machine utilized in treatment are produced by Nucletron (Elekta AB, Stockholm, Sweden). (Figures 1-2).

Iridium-192 source was used in a single intracavitary application with a dose rate of 0.5 Gy/hour to the envelope. The treatment duration ranged from 30-70 hours during which patients were admitted to the BT unit. Tandem and ovoids applicators were used. The envelope and subsequently the length and position of vaginal sources, and the time the source is stepping in each dwell position were individualized for each patient based on the tumor topography, and the patient’s anatomy in order to optimize the treatment plan. During each insertion, whenever possible, a rectal retractor and anterior vaginal packing were used to maximize the distance between the sources and the anterior rectal wall and posterior bladder.

Figure 1: A case of stage IIB Squamous cell carcinoma of the cervix, initial tumor volume was 70 cc. An envelope is drawn around the TV and an isodose line encompassed this envelope (127 cc). The patient received a 50Gy pulse/hour for 40 hours delivering total of 20 Gy to the entire envelope. The reported max and mean rectal doses were 19.75 and 18.41 Gy and the max and mean bladder doses were 19.75 and 17.67 Gy respectively.

Figure 2: A case of stage IIB Squamous cell carcinoma of the cervix, initial tumor volume was 44 cc. An envelope is drawn around the TV and an isodose line encompassed the envelope. Treatment unit: Ir-192-mPDR, treatment unit type: microSelectron PDR, Nucletron source: Ir-192-mPDR, Isotope: Ir-192, Air Kerma strength: 2410.001 cGy/Gy cm2, Reference exposure rate: 2478.888 R/h cm2, Apparent source activity [mCi]: 592.397 mCi, Apparent source activity [MBq]: 21644.99 MBq, Air Kerma rate constant: 4.86200 cGy/h / mCi * cm2, Step size: 5.0 mm, Air Kerma strength: 623.444 cGy/h cm2, Interval between irradiation and treatment date/time: 143.98 days, Decay factor: 0.259.

Follow-up: During treatment, all patients had weekly clinical examinations as well as laboratory tests. Patients’ follow-up was performed one month after treatment completion then every 4 months in the first two years and twice a year in the next 3 years. Thorough history taking and physical examination including gynecological examination was performed at each follow-up visit. Imaging studies (CT images, MRI and/or FDG-PET) were obtained as indicated to detect any possible local-regional recurrence or distant metastases. Treatment induced AEs including hematological toxicities, acute and chronic gastrointestinal and genitourinary toxicities and fatigue were closely monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC AE), version 4.0. Local control (LC) rate, distant metastases (DM) rate, progression free survival (PFS) and overall survival (OS) for all patients and stratified by various patients and tumor characteristics are reported in this study.

RESULTS

Patient and tumor characteristics:

This study included 96 patients diagnosed with locally advanced cervical cancer and treated consecutively from January 2006 to December 2008 who met all the inclusion criteria. The median age of patients is 50 years (range 25 to 82 years).

Characteristics | N | %
--- | --- | ---
Age | | |
25 – 39 | 17 | 17.9
40 – 49 | 30 | 31.6
50 – 59 | 26 | 27.4
60 – 69 | 11 | 11.6
70 – 85 | 11 | 11.6
Smoking | | |
Non-smoker | 74 | 77.9
Ex-smoker (stopped > 10 years ago) | 11 | 11.6
Smoker | 10 | 10.5
Tumor Stage | | |
IB1 | 1 | 1.1
IB2 | 28 | 29.5
IIA | 2 | 2.1
IB | 30 | 31.6
IIA | 2 | 2.1
IIIB | 32 | 34.5
Lymph node Status | | |
Negative | 59 | 62.1
Positive Pelvic only | 19 | 20
Positive Para-aortic only | 1 | 1.1
Positive Pelvic and Para-aortic | 16 | 16.8
Tumor Size in cm | | |
< 5 cm | 48 | 50.5
≥ 5 cm | 47 | 49.5
Treatment Field | | |
Pelvis | 78 | 82.1
Pelvis and Para-aortic | 17 | 17.9
Radiation Therapy:
The mean EBRT dose was 45 Gy (range 40 – 50 Gy). Forty patients (42%) had Parametral boost, the median dose was 15 Gy (range 4 – 14 Gy). The median BT dose prescribed to the envelope was 20 Gy (range 15 – 35 Gy) that was delivered 0.5 Gy / hour. The range of maximum rectal dose reported during BT was 7.8 – 24.2 Gy (median 17.5 Gy) and the median dose range was 5.1 – 18.4 Gy (median 13.9 Gy). The range of maximum bladder dose reported during BT was 9 – 35.5 Gy (median 21.4 Gy) and the median dose range was 5.7 – 22.9 Gy (median 16.8 Gy). The median volume encompassed by 60 Gy isodose curve (V60Gy) was 137 cc (range 26 – 365 cc).

TREATMENT–INDUCED ADVERSE EVENTS:

Toxicity | Grade 1 / 2 | Grade 3 / 4 | N | % | N | %
--- | --- | --- | --- | --- | --- | ---
Anemia | 5 | 5.3 | 11 | 11.6
Neutropenia | 4 | 4.2 | 13 | 13.7
Thrombocytopenia | 0 | 0 | 1 | 1.1
Acute gastrointestinal toxicity | 14 | 14.7 | 11 | 11.6
Chronic gastrointestinal toxicity | 5 | 5.3 | 3 | 3.2
Acute genitourinary toxicity | 9 | 9.5 | 3 | 3.2
Chronic genitourinary toxicity | 4 | 4.2 | 4 | 4.2
Fatigue | 10 | 10.5 | 3 | 3.2

CONCLUSIONS

Definitive CRT followed by PDR BT boost is an effective and tolerable treatment modality for bulky cervical cancer. PDR BT provides some radiobiological advantages over high dose rate BT that might lead to better toxicity profile and superior treatment outcomes. Volume based 2D planning set the concepts and paved the way to the modern image-guided brachytherapy (IGBT). IGBT would potentially lead to improvement of local control, improvement of cure and minimize treatment induced adverse events, still it needs to provide valid clinical evidence of better toxicity profile and superior survival advantage compared to the conventional 2D planning.