Outcomes of Computed Tomography-Guided Image-Based Interstitial Brachytherapy for Cancer of the Cervix Using GEC-ESTRO Guidelines

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Abstract

Locally advanced cancer of the cervix is treated by concurrent chemoradiation followed by brachytherapy. Interstitial brachytherapy is used to treat large tumors with involvement of parametrium, post-hysterectomy, and narrow, conical vagina. The GYN GEC-ESTRO working group described target volume delineation and also 3D image-based planning using MRI and 3D dose-volume parameters for brachytherapy of carcinoma cervix. CT-based as compared to MR-based image-guided brachytherapy (IGBT) is much more feasible and practical because MR access is still difficult for most departments. This is a retrospective study done to assess the local control in cancer of the cervix, treated based on these guidelines and dose received by 2 cm³ of the rectum as defined by the GEC-ESTRO guidelines and its correlation with long-term toxicity. Sixty-three patients of cancer of the cervix received 45 Gy/25 fractions of external beam radiotherapy with concurrent weekly cisplatin followed by interstitial brachytherapy. A central tandem was inserted into the uterine cavity. The needles were inserted based on the concept of gross tumor volume (GTV), high-risk clinical target volume (HRCTV), and intermediate-risk CTV (IR CTV) as defined by the GYN GEC-ESTRO guidelines. All patients underwent CT-based planning. A dose of 6.5 Gy × 4 fractions was delivered in two sessions such that the HRCTV received a total dose of 26 Gy. Dose optimization was done to prevent 2 cm³ of rectum from receiving > 400 cGy (60% of prescribed dose) per fraction and 2 cm³ of bladder from receiving 500 cGy per fraction. At a median follow-up of 41.5 months (range 6–106 months), 74.6% (47/63) of the patients were alive, with no local, loco-regional, or distant metastasis. Loco-regional control rate was 88% (56/63). Eight percent (5/63) of the patients developed grade I proctitis which was managed conservatively. There was no grades II, III, or IV proctitis. There was no bladder or sigmoid toxicity. GEC-ESTRO guidelines can be modified for CT-based planning also with very minimal late toxicity without compromising local control.

Keywords GEC-ESTRO guidelines · Cervical cancer · Image guided brachytherapy

Introduction

Cancer of the cervix continues to be an important cause of morbidity in India and other developing countries. In India,

it is the second commonest cancer, accounting for nearly 23% of all cancer cases in women and the third most common cause of death. In India, about 123,000 new cases of cancer of the cervix are diagnosed every year and about 68,000 women die as a result of the disease [1]. Cancer of the cervix when detected early has a very high 5 year survival rate of about 91% [2]. Early cancer of the cervix (stages Ia, Ib, and IIa) is treatable by surgery alone, although radiotherapy is also an equally good alternative for those patients who refuse surgery or are not medically fit to undergo surgery [3]. But the standard of care for locally advanced cervical cancer (stages IIb, III, and IVa), following the National Cancer Institute alert, supported by long-term results, is concurrent chemoradiation [4–10].

Brachytherapy is an integral part in the optimal management of cervical cancer. No amount of high-precision external radiotherapy has been able to replace brachytherapy in cancer of the cervix. The foremost advantage of brachytherapy is the

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rapid dose fall off which allows a very high dose to be delivered to the tumor while sparing the organs at risk (OARs), i.e., the bladder, rectum, sigmoid colon, and small bowel. Low dose rate (LDR) or high dose rate (HDR) brachytherapy can be used for treatment and there is evidence that there is no difference in overall survival, local recurrence, or late complications between the two [11, 12]. Most centers now prefer HDR brachytherapy for its convenience to the patient, shorter treatment times, and opportunity for dose optimization.

In early stage cervical cancer, where the disease is confined primarily to the cervix, intracavitary brachytherapy has been the preferred technique of application. The tandem and ovoid applicators or the tandem and ring applicators provide pear-shaped isodose lines which encompass the uterine cavity, cervix, and upper vagina, thus providing adequate dose to achieve high local control. However, the local control rate declines significantly for large tumors, and especially for tumors with unfavorable topography in relation to this pear-shaped dose distribution which is inadequate to encompass the disease involving the parametria or lower vagina [13]. Interstitial brachytherapy is recommended in such situations as well as when a patient has a narrow and conical vagina precluding optimal intracavitary application or for treating the vaginal vault following hysterectomy [14].

Traditionally, to achieve adequate dose to the cervix with an intracavitary application, the dose is prescribed to a point, in the dose-limiting region of the paracervical triangle, called point A. However, the definition of point A has not remained constant and has varied over the years [15, 16]. As a result, point A has been a less reliable and less reproducible point and the dosimetric changes due to variations in point A definitions have been up to 11–12% [17]. In an ideal application, the tandem bisects the height of the ovoids and is equidistant from the ovoids. However, commonly, the patients' anatomy or physician's lack of experience can lead to suboptimal application. Potish showed that lateral displacement of colpostats in the frontal plane, vertical separation between colpostat and tandem, and anterior-posterior displacements of colpostats relative to tandem greatly affected the traditional calculation points [18].

The GYN GEC-ESTRO working group described target volume delineation and also 3D image-based planning and 3D dose–volume parameters for brachytherapy of carcinoma cervix [19, 20]. The planning was done on magnetic resonance (MR) images, which was useful in identifying the gross disease and the organs at risk with clarity. The advantage of this method is that it follows volume-based planning thus moving away from the reliance on point A. Following these reports, many centers are increasingly changing over to 3D image-based planning from 2D X-ray-based planning. It has been shown recently that more than 87 Gy of dose is needed to

the high-risk areas (cervix and any residual disease at time of brachytherapy) to attain local control rate of more than 90% and this can be achieved with image-based brachytherapy without any increase in radiation-induced morbidity [21, 22].

Late rectal toxicity has been the major concern in patients of cervical treated with a combination of external beam and brachytherapy. Radiation proctitis occurs primarily due to contribution to rectal dose during brachytherapy. With 3D volume-based planning, dose received by various volumes of rectum can be assessed. The GYN GEC-ESTRO working group has described 3D image-based contouring of OARs and analysis of dose–volume histogram (DVH) parameters based on the contoured volume. They have recommended a minimum dose for the most irradiated tissue volume of 0.1 cm³ (D0.1cc), 1 cm³ (D1cc), and 2 cm³ (D2cc) for the rectum to be reported [19, 20, 23, 24]. The EMBRACE trial showed that a D2cc < 65 Gy is associated with minor grade less frequent rectal morbidity, whereas a D2cc > 75 Gy is associated with higher grade and more frequent rectal morbidity [25].

With the widespread availability of CT simulators within the radiation oncology departments, CT-based as compared to MR-based image-guided brachytherapy (IGBT) is much more feasible and practical because MR access is still difficult for most departments. CT/MR compatible applicators and interstitial needles are easily available. Moreover, with the availability of CT contouring guidelines [26, 27], recently, the use of this modality in this role has gained momentum.

Since 2008, we have followed 3D CT-based brachytherapy planning for carcinoma cervix as per the GEC-ESTRO guidelines. This is a retrospective study done to assess the local control in cancer of the cervix, treated based on these guidelines and dose received by 2 cm³ of the rectum as defined by the GEC-ESTRO guidelines and its correlation with long-term toxicity.

Materials and Methods

Patient Characteristics

Sixty-three consecutive patients with histopathologically proven cancer of the cervix treated at Department of Radiotherapy, Manipal Hospital Bangalore, between 2008 and 2014, were taken up for the study. Patients were staged as per the International Federation of Obstetrics and Gynecology (FIGO) staging system. The staging was done by clinical examination without anesthesia. Patients also had a chest X-ray, ultrasound abdomen and pelvis, complete blood counts, and renal function tests before the start of the treatment. The gross disease extent before treatment was documented.

Radiotherapy Details

External Radiotherapy

All patients received external radiotherapy to the pelvis, to a dose of 45 Gy in 25 fractions, given once a day for 5 days in a week. They also received once a week cisplatin 40 mg/m² concurrent with radiation. Patients with enlarged paraaortic nodes received neoadjuvant chemotherapy followed by concurrent chemoradiation. All patients underwent CT simulation with intravenous contrast. During simulation, a bladder protocol was followed wherein the patient was first asked to empty her bladder and then made to drink 500 ml of water. CT simulation was done 45 min later. The same protocol was followed during treatment to ensure comfortable and reproducible bladder filling.

CT images were transferred to the contouring workstation (Varian Eclipse—Palo Alto, CA). Target volumes were delineated based on established contouring guidelines [26–28]. If paraaortic nodes were found to be enlarged, then the nodal volume was extended to include the lower paraaortic nodes up to the renal hilum. The planning target volume (PTV) was obtained by combining the primary clinical target volume and the nodal volume and expanding the combined volume by 7 mm. This margin was obtained based on our own data of set-up errors. Patients were treated by 3D conformal radiotherapy and in all cases 95% of the PTV received $\geq 95\%$ of the prescribed dose. Brachytherapy was scheduled within 2 weeks of completion of external radiotherapy for all patients.

Brachytherapy

All patients underwent interstitial brachytherapy (ISBT) under general anesthesia. Patients were examined under anesthesia and the disease response was documented. Needles were inserted transperineally using Syed Neblett Gyn perineal template. A central tandem was inserted into the uterine cavity if the cervical os could be sounded and dilated. The needles were inserted based on the concept of gross tumor volume (GTV), high-risk clinical target volume (HRCTV), and intermediate-risk CTV (IR CTV) as defined by the GYN GEC-ESTRO guidelines.

The implant was done in two sessions with a maximum interval of 2 weeks between sessions. Two fractions of HDR brachytherapy were delivered during each session with a minimum of 4-h interval between each fraction. In the first session, the needles were inserted to cover the initial disease at diagnosis (GTVD), irrespective of the extent of response. The needles thus encompassed the entire cervix, residual tumor at the time of brachytherapy (GTVB), and the initial tumor extent at diagnosis (HRCTV). A margin was given beyond the HRCTV for possible microscopic spread and this volume constituted the intermediate-risk CTV (IR CTV). In the second

session, the needles were inserted to cover only the cervix and residual tumor at the time of brachytherapy.

All patients underwent CT simulation following the implant. The bladder was filled with 50 ml of diluted contrast for delineation. Twenty milliliters of diluted contrast was pushed into the rectum to delineate rectum and sigmoid colon respectively. To maintain consistency, 50 ml of saline was used to fill the bladder during treatment as well.

The bladder, rectum, and sigmoid colon were contoured as the OARs on 3-mm axial slices. Target volume was delineated by contouring around the needles. The entire uterus was not contoured as a target volume, but a uniform area of 2-cm diameter around the central tandem was treated to the prescription dose. The same procedure was followed for the second session as well.

Planning

All patients received a dose of 6.5 Gy $\times$ 4 fractions (in two sessions) such that the HRCTV received a total dose of 26 Gy. Varian Eclipse (Palo Alto, CA) system was used for brachytherapy planning. The DVH parameters that were evaluated were the dose to 2-cm³ volume of the rectum, bladder, and sigmoid and the dose to 90% of the target volume (D90), dose to 100% of the target volume (D100), and volume receiving 100% of the dose (V100).

Dose optimization was done to prevent 2 cm³ of rectum from receiving > 400 cGy (60% of the prescribed dose) per fraction and 2 cm³ of bladder from receiving 500 cGy per fraction. The dose constraints for the sigmoid were similar to those of the rectum.

Follow-Up

Patients were called 15 days after completion, to assess for any acute reactions. Subsequent follow-up was done at 1 month, then 2 months for the first 2 years, 3 months in the third year, every 6 months up to 5 years, and annually thereafter. During each follow-up, clinical history was taken and general physical examination, abdomen examination, and speculum and bimanual pelvic examination were done. All patients who had a minimum follow-up of 6 months from the last day of treatment were considered for the analysis. Rectal toxicity was graded as per the EORTC-RTOG late toxicity criteria.

Results

Sixty-three patients were available for a final analysis with a median follow-up of 41.5 months (range 6–106 months) from the date of completion of brachytherapy. The median age was 54 years (range 25–80 years). The FIGO stage distribution

was as follows: stage Ib—7 patients; stage II—30 patients; stage III—22 patients; and stage IVB—4 patients.

Fifty-nine patients (93.6%) received concurrent chemotherapy. Four patients received neoadjuvant chemotherapy as three of them had paraaortic nodes at diagnosis (stage IVB) and one patient at the discretion of the referring physician.

The mean D2cc, D1cc, and D0.1cc were 72 ± 3.5 Gy, 74 ± 3 Gy, and 80 ± 4 Gy respectively. There were no adverse events with respect to the bladder and sigmoid colon and hence their toxicity and dose correlation were not assessed.

Loco-Regional Recurrence

At the time of analysis, 74.6% (47/63) of the patients were alive, with no local, loco-regional, or distant metastasis. Loco-regional control rate was 88% (56/63). Eight patients developed distant metastases. The sites of distant metastases were lung, bone, or supraclavicular nodes. At the time of analysis, six of the eight patients were alive on palliative chemotherapy and two patients had died of the disease. Two patients died due to loco-regional recurrence, at 19 and 24 months, after completion of treatment. One patient had a residual disease after brachytherapy which at the time of analysis had progressed loco-regionally. This patient had received neoadjuvant chemotherapy as a preference of the referring physician but did not receive concurrent chemotherapy. One patient developed second malignancy which was diagnosed as metastatic carcinoma breast. She had no local disease in the cervix.

There was no correlation of recurrence with the stage of the disease.

Rectal Toxicity

Eight percent (5/63) of the patients developed grade I proctitis which was managed conservatively. There was no grades II, III, or IV proctitis. Of the patients with grade I proctitis, only one patient had received a total dose of 75 Gy to 2 cm³ of the rectal volume whereas in all others the dose to 2 cm³ rectum was less than 75 Gy. There was no correlation with the stage of the disease.

There was no bladder or sigmoid toxicity.

Discussion

In intracavitary brachytherapy for carcinoma cervix, radiotherapy has been historically delivered to point A. Although this has proven to be effective in achieving local control, there are certain limitations in prescribing to point A. The planning is done two-dimensionally on orthogonal X-rays and there is no scope for optimization of dose. A dose prescribed to point A would always result in a fixed dose at a fixed distance from

the cervical os, regardless of the size or shape of the residual mass at the time of brachytherapy. Variations in anatomy and applicator position are other factors which can result in varied doses to point A.

The GEC-ESTRO guidelines introduced the concept of 3D image-guided brachytherapy and 3D dose–volume parameters for brachytherapy of carcinoma cervix [19, 20]. The recommendations of GEC-ESTRO were for MRI-based intracavitary brachytherapy. Long-term results from these studies have shown that DVH parameters of D2cc for the rectum, sigmoid, and bladder have a predictive value in assessing late toxicity and statistically significant difference was noted when this was compared with the ICRU dose points [23]. Application of these guidelines has shown improved DVH parameters for dose coverage as well [24]. Potter et al. have shown > 85% local control and low treatment morbidity by using MR-based planning [22]. In general, IGBT clinical experience indicates a very favorable therapeutic ratio with high local control rates (> 90%), even for advanced disease applying high target doses (> 90 Gy), and in parallel with low morbidity rates (< 5% G3/G4). The retroEMBRACE trial showed a 3/5 actuarial local control in excess of 89% for stage III and 96% for stage II [29].

In India, majority of patients with cancer of the cervix present with advanced parametrical disease which makes interstitial brachytherapy a more reasonable option. MRI has shown to be superior in tumor volume delineation as compared to clinical examination and CT scan. MRI though is still an expensive imaging modality and is not widely available in our country. Therefore, it is prudent to use CT scan routinely in brachytherapy planning. We therefore incorporated these guidelines to CT-based interstitial brachytherapy and analyzed the outcomes.

CT-Based Planning

Vishwanathan et al. [27] compared MRI- and CT-based contouring in a prospective trial and concluded that CT contours significantly overestimated the tumor width as compared to MRI but they noticed no difference in OAR DVH analysis. MRI remains the standard for GTV delineation. At our center, we defined the gross tumor clinically. The gross extent is noted before the start of external beam radiotherapy and at the time of brachytherapy. This extent of disease guides the placement of needles during interstitial brachytherapy. The limitation of poor target volume delineation with CT was taken care of by placement of the needles and tandem as we were aware of the extent of disease.

The needles were implanted to cover the volume as defined by GEC-ESTRO. In the first session, the needles and central tandem covered the initial extent of the disease (disease extent before external radiation). This included both the high-risk

and intermediate-risk CTV. During the second session, the needles were implanted to cover the residual disease at the time of brachytherapy only (HRCTV). Contouring was done on CT by marking around the needles which represented the CTV.

We included the entire uterine canal in our treatment as the intrauterine extension was unknown in majority of the cases due to a lack of MRI at the time of diagnosis [30]. This combination of intracavitary and interstitial application allows better dose distribution and optimization to cover the target volume. Recent analysis of the retroEMBRACE trial has shown that this approach improves the therapeutic ratio [29].

Local Control

Our local control rate is about 88% at a median follow-up of 41.5 months (range 6–49 months) which is comparable to studies which have used MRI for planning [22, 25]. Our local control rates by stage have been at par with the rates reported in literature. For stage II, we have seen a local control of close to 93% and for stage III it is 90% which are better than most reported series thus proving that our method does not compromise local control.

Late Toxicity

Our grade I rectal toxicity is around 8% (3/29) with no grades 2, 3, or 4 toxicity. There were no bladder or sigmoid toxicity which makes our technique extremely safe. We have been conservative with the OAR doses and the reason for that is the plane between the rectal and bladder walls and vagina is not clearly defined on CT and there are artifacts due to the use of steel needles which reduces the clarity further. Despite the preference given to the OARs, we have shown that our local control rates have not been compromised. With conventional planning, historically, there used to be high rate of sigmoiditis since the dose to sigmoid could not be evaluated. We contoured the sigmoid and by optimization could control the dose. Hence, there were no adverse effects with sigmoid. Similarly, we observed no late bladder effects as well. Studies such as the retroEMBRACE analysis had 5-year grades 3–5 toxicity of 5–7% [29, 31]. Ribiero et al., in their 10-year follow-up, noticed 12% (21 patients) had grades 3 and 4 toxicity, of which 6% were bladder and 2% sigmoid, whereas we had none [32].

The limitations of our study are the probable overestimation of the treatment volume since we did not have a MRI scan, but we have felt that it is better to over-treat than have a failure.

Conclusion

CT-based image-guided brachytherapy is very useful in delineating the OARs and target volumes. DVH parameter of D2cc volume correlates well with late effects. We have shown that with GEC-ESTRO guidelines can be modified for CT-based planning also with very minimal late toxicity without compromising local control.

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