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Dosimetric Outcomes of Three Dimensional Conformal Radiation therapy and Intensity Modulated Radiation therapy coplanar Plans for Patients with Glioblastoma Multiforme (GBM)

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Abstract

The aim of the present study is to evaluate the dosimetric analysis of doses received by planning target volume and organs at risks by using intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3D-CRT) techniques in patients treated for glioblastoma multiforme. A total of ten patients underwent computed tomography treatment planning in conjunction with magnetic resonance imaging fusion. Prescription dose and normal-tissue constraints were identical for the 3DCRT and IMRT plans. All the Patients were treated on Clinac DHX Linear Accelerator. The prescribed dose was 60 Gy delivered at 2.0 Gy per fraction using 6 MV photons. The tolerance level for maximum dose was 7.0 Gy for lenses and 54.0 Gy for brain stem, optical chiasm and optical nerves as per RTOG criteria. The Target volumes, organ at risk (OAR), dose volume constrains were used for planning. Cumulative dose volume histogram of target volumes and organ at risk (OAR), normal brain tissue integral dose, target coverage, target homogeneity, target conformity, and normal tissue sparing with 3DCRT and IMRT planning were compared. Statistical analysis was performed to determine the differences. A statistically significant difference between 3DCRT and IMRT and in the mean dose to the PTV ($p < 0.519$) has been observed. The mean value of the PTV was 61.04 ± 1.152 in 3DCRT and 60.72 ± 1.005 in IMRT. The maximum dose to the PTV in 3DCRT (64.26 ± 2.36) and in IMRT (62.95 ± 2.33) had a lower maximum dose to the PTV ($p = 0.228$). This result indicates that IMRT was better than 3DCRT. The average minimum dose in IMRT was (46.80 ± 3.89) compared to (49.06 ± 4.98) in 3DCRT, ($p = 0.285$). The dose to 95% of the PTV was (57.73 ± 1.55) in IMRT to (58.20 ± 0.97) in 3DCRT, ($p = 0.423$). Conformity index (CI) was approximately equal in both modalities with an average value of 0.962 ± 0.041 in IMRT compared to (0.969 ± 0.039) in 3DCRT, ($p = 0.481$). The average homogeneity index (HI) in IMRT was 0.187±0.176 and 0.099 ± 0.050 in 3DCRT, ($p = 0.165$). Therefore, IMRT achieved an improvement in HI. Target coverage index (TCI) in IMRT was 0.7213 ± 0.2050 and 0.5970± 0.194 in 3DCRT. The IMRT plan yielded superior target coverage and reduced radiation dose to the brain, brainstem, and optic chiasm. With the availability of new cancer imaging tools and more effective systemic agents, IMRT may be used to intensify tumor doses while minimizing toxicity, therefore potentially improving outcomes in patients with high-grade glioma.

Keywords: Glioblastoma multiforme (GBM), Intensity modulated radiation therapy (IMRT), Three dimentional conformal radiation therapy (3DCRT).

Introduction

Treatment for malignant gliomas typically requires a combined approach that includes surgery, radiotherapy and chemotherapy. Radiotherapy is an important adjuvant treatment for malignant gliomas. Intensity-modulated radiotherapy (IMRT) has been demonstrated to be superior to three-dimensional conformal radiotherapy (3D-CRT) in patients with malignant gliomas.[1-3] The treatment of malignant gliomas after surgery has been

reported to significantly prolong patient survival.[4-6] With the introduction of modern techniques like Three Dimensional Conformal Radiation therapy (3D CRT) and Intensity-Modulated, the use of Radiation therapy (IMRT) is increasing in clinical practice.[7-9] Modern radiotherapy techniques such as 3D CRT and IMRT significantly increase the dose to the tumor and reduce the dose to the normal tissue.[10-12]

Intensity modulated radiation therapy (IMRT) uses computed tomography based planning and delivery of radiation, and with the help of TPS improves the dose to target , while minimizing doses to organs at risk (OAR), it can provide significantly better tumor target coverage and sparing of sensitive normal tissue compared with 3D CRT.[13-14] Such modern techniques use modern medical imaging techniques, efficient dosimetric software, accurate patient positioning methods, stringent verification and quality control of procedures, which increases tumor control by boosting tumor dose, reducing morbidity and sparing healthy tissues.[15] Three dimensional conformal radiation therapy uses computed tomography planning to generate 3D volumes of a patients' anatomy. In 3D CRT, multiple beams at various angles are projected towards target in such a way that the intended dose will be delivered to the target while relatively sparing critical structures. 3D CRT often produces unacceptable plans for concave or irregular targets that are close to critical structures.[16] In Intensity modulated radiation therapy (IMRT) dynamic or static multileaf collimators are used for dose optimization and thus delivers highly conformal dose to target while sparing the surrounding normal structures. The multileaf collimator can be in a "dynamic" or "static" form. In the dynamic form, the leaves at each gantry position are swept across the target while the beam is on and their speed determines the radiation fluency. In static or segmental multileaf IMRT, each field consists of multiple segments with different intensities. These forms of IMRT are currently offered by most manufacturers of linear accelerators.[17-19] Intensity modulated radiation therapy (IMRT) requires additional clinician input for delineating target volumes and more robust physics actions has to be performed. Assessment of the risks and benefits of IMRT is therefore important in determining its clinical utility.[17] The dose-volume-histogram (DVH) is a common tool used in both IMRT and 3D CRT to evaluate dose conformity and homogeneity to target and at the same time this tool gives information about the dose received by the critical structures. DVHs do not provide spatial information such as the location of the high- and low-dose regions ("hot" and "cold" spots) inside the volume of interest (VOI).[18] Patient-specific quality assurance (QA) is used to verify the dose mapping given by the treatment planning system (TPS). Verification procedures for 3D conformal radiation therapy (3D CRT) and intensity-modulated radiotherapy (IMRT) are commonly performed for an individual patient.[19]

Materials and Methods

2.1. Planning Systems and Radiotherapy Machine

Clinac DHX was the linear accelerator used for present study. It has 40 pairs of multi leaf collimators, the width of each leaf when projected at the isocenter is 10 mm. This linear accelerator has two modes of treatment, photon mode and electron mode. In this study only photon mode with 6 MV energy is used. The treatment planning system was the external beam planning system of Eclipse (Varian Medical System) and the volume calculation used was the Anisotropic Analytical Algorithm (AAA).

2.2. Acquisition and Simulation

Planning CT scans were taken on Somatom Sensation Siemens CT Simulator with patients in supine position and immobilized with a three clamp orfit cast. Imaging acquisition protocol required a slice thickness of 3 mm in a multislice CT scanner, both immediately (within 15 s) and delayed, in other words, 10 min after injection of contrast. The images were then transferred to the Eclipse™ treatment planning system (v. 13.2, Varian Medical Systems, CA, USA). Planning CT images were fused with postoperative magnetic resonance (MR) images that were taken a few days before starting the radiation. The target and other OAR's were contoured following RTOG protocol. The gross tumor volume (GTV) included postoperative cavity and gross residual tumor seen on the CT images and fused MR images. The clinical target volume (CTV) includes 2.0 cm isotropic margin all around the GTV along with edema surrounding the tumor following anatomical boundaries. PTV was generated by giving a 0.5 cm symmetrical margin around the CTV. OARs, including the optic chiasm, right and left optic nerves, right and left temporal lobes, brain stem, right and left eye, right and left lens and right and left cochlea, were contoured.

Plans were optimized to deliver prescribed dose to more than 95% of PTV and maximum dose in the target volume not to exceed 107% of prescribed dose international commission on radiation units and measurements (ICRU) : 50 and 62. Dose volume histograms were generated for qualitative and quantitative assessment of generated plans and evaluated for all the OARs before delivering treatment. Evaluation of dosimetric data was done, in other words, doses received by target volumes and OARs using Quantitative Analysis of Normal Tissue Effects in Clinics (QUANTEC). If the dose constraints of OARs were not met, depending on the location and burden of the tumor, we prioritized the OARs surrounding the tumor and plans were optimized accordingly, for example, for tumors close to or invading the left optic nerve, instead of under dosage, we have preferred treating till 60 Gy after prioritizing the right optic nerve to preserve vision. All 3D-CRT plans were analyzed in terms of PTV coverage, conformity index (CI), homogeneity index (HI) and OAR dose volume parameters, as per ICRU 83.

2.3. Conformal Planning

Treatment plans were created with 6 MV photons. All fields were shaped at the beam's eye view to encompass the PTV shape using multileaf collimator (MLC). The treatment target volume included the PTV and an additional 0.7-cm margin for beam penumbra in all directions. The treatment field's isocenter was positioned in the center of the PTV and the calculation point was taken at the treatment field's isocenter. Physical wedges (PW) and virtual wedges (VW) were used to modify the dose in the treatment plan and to perform dose homogeneity in PTV.

2.4. Inverse-Planned IMRT

Treatment plans were created for 6-MV photons with the same TPs with objective functions based on physical constraints. IMRT plans were generated using commercial inverse planning software. The beams are spread around the target with equispace and to avoid the opposing fields an odd numbers of the treatment fields were used.

2.5. Treatment Planning Evaluation Tools

The TPS used for this study (Eclipse 13.2) have many tools for qualitative and quantitative evaluation of the treatment plans. The visual slice by slice review of the treatment plans using isodose lines distribution can be used as a qualitative evaluation for the treatment plans. The qualitative evaluation is important to know the location of the hot and cold areas in the treatment plans. The quantitative evaluation included the maximum, minimum, mean doses and DVHs. Dose Volume Histogram (DVH) was generated to evaluate the dose to the different structures in different treatment plans. For PTV, the parameters, D98%, D95% and D2% were used for plan evaluation, where D98% and D2% values are defined as the dose received by 98% and 2% of the PTV volume these two values are represented the maximum and minimum doses in the PTV, D95% is target volume covered by 95% of the prescribed dose, for OARs, the mean and maximum dose for brain stem, optic nerve and lenses were used for treatment plan evaluation.

2.6. Comparative evaluation of treatment plans

In this study, dosimetric analysis of 3D CRT and IMRT plans was performed for each of the 10 patients by both qualitative and quantitative measures. Isodose distribution was first compared visually on axial, sagittal and coronal slices for degree of conformity of the prescribed dose to the PTV and then for any inclusion of OAR within high dose and low dose levels. Specifically, we examined isodose lines from 5 Gy and up in our evaluation. Direct comparison was also made of the cumulative DVH curves for PTV, OAR, and non-target tissue. Integral dose to non-target brain tissue (Brain-PTV) was evaluated. Plan comparison was also made quantitatively by comparing DVH parameters and by computing and comparing relevant metrics for target coverage, target conformity, dose heterogeneity within the target, and critical normal tissue sparing. Target coverage was assessed by comparing the minimum and maximum doses to PTV (D_{min} and D_{max} respectively).

The dosimetric evaluation metrics used to compare the two plans, in terms of mean, maximum and minimum doses to PTV, were dose to 95% of PTV, Homogeneity Index (HI), Conformity Index (CI), Target Coverage Index (TCI) and Mean and maximum doses to critical organs and normal tissue. The dose to 95% of the PTV (D95%) was used to quantify PTV coverage. The homogeneity index (HI) was used to evaluate uniformity (homogeneity) of dose within the PTV and is calculated as

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad (1)$$

Where $D_{2\%}$ and $D_{98\%}$ represent the doses to 2% and 98% of the PTV, respectively. For example, D98 indicates that at least 98% of the target volume receives this dose, and hence $D_{2\%}$ and $D_{98\%}$ are considered to be the maximum and minimum doses, respectively.

The conformity index (CI) was also calculated and can be defined as the degree of conformity of the plans, which is a ratio of the PTV receiving 95% of the prescribed dose divided by the volume of the PTV. A CI value approaching 1 indicates a higher degree of conformity.

$$CI = \frac{PTV_{95\%PD}}{V_{PTV}} \quad (2)$$

The target coverage index (TCI) accounts for the exact coverage of PTV in the treatment plan at the prescribed dose as shown below:

$$TCI = \frac{PTV_{PD}}{PTV} \quad (3)$$

Where PTVPD is the PTV coverage at the prescribed dose (PD) and PTV is the volume of PTV. Target conformity index reports target dose coverage as a value between 0 and 1. A value of 1 indicates an ideal plan with target coverage by prescribed dose. However, a TCI value of 0 indicates the whole target volume is not covered by the prescribed dose [20-21].

Statistical Analysis

Statistical analysis was done using a paired two-tailed student't' test. The test was applied to calculate the difference between two means. A value of $p \leq 0.05$ was considered to be statistically significant.

Results

Differences were recorded between those patients who planned with 3D CRT and those who planned with IMTR. Thus one patient was selected to represent all other patients in this site for isodose distribution comparison, dose volume histogram (DVH) comparison, dosimetric results for the PTV and dosimetric results for the critical organs. DVHs figures include the PTV and critical organs for each modality and show the percentage of the total volume (y-axis) of each ROI receiving a specified dose (x-axis) in units of Gy.

3.1. Glioblastoma (GBM) Cancer

Ten patients whose diagnosis with GBM received 60 Gy per 30 fractions given once daily five days per week over a period of six weeks were included in this study. CT Scans were performed for the whole brain on a CT scanner with 0.3 cm slice thickness. The patients were positioned supine, and straight and level. A warm wet sheet of plastic mesh was placed over the face to fit around the head and was

Table 1.1: Evaluation metrics for PTV in terms of D_{MEAN}, D_{max} and D_{min} covered 95% of the target

Patient Code	D_{mean}(Gy)		D_{max}(Gy)		D_{min}(Gy)		$D_{95\%}$(Gy)	
	3DCRT	IMRT	3DCRT	IMRT	3DCRT	IMRT	3DCRT	IMRT
01	60.00	61.21	64.88	62.36	52.58	53.70	58.10	57.60
02	61.15	60.50	67.18	67.00	54.46	51.70	59.10	57.00
03	60.00	59.75	68.28	64.53	47.52	39.70	56.21	58.29
04	62.00	60.00	64.00	63.80	41.50	44.19	57.40	54.23
05	59.72	60.68	62.53	61.3	56.72	50.09	58.23	59.57
06	60.02	59.32	65.43	64.47	41.87	48.00	59.30	58.00
07	61.00	62.08	63.50	62.50	46.11	46.60	58.11	59.70
08	61.00	59.88	64.63	64.00	49.45	43.60	59.50	58.50
09	63.00	62.00	61.50	60.00	50.60	45.50	58.20	57.50
10	62.53	61.90	60.75	59.45	49.86	44.95	57.80	56.92
Mean	61.04±1.15	60.72±1.00	64.26±2.36	62.95±2.33	49.06±4.98	46.80±4.16	58.20±0.97	57.73±1.55
P-value	P<0.519		P<0.228		P<0.285		P<0.423	

Table 1.2. Evaluation metrics for the PTV in terms of CI, HI and TCI

Patient Code	$CI = \frac{PTV_{95\%PD}}{V_{PTV}}$		$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$		$TCI = \frac{PTV_{PD}}{PTV}$	
	3DCRT	**IMRT**	**3DCRT**	**IMRT**	**3DCRT**	**IMRT**
01	1.00	0.94	0.06	0.16	0.82	0.68
02	0.99	0.98	0.10	0.14	0.85	0.81
03	0.90	0.99	0.17	0.66	0.46	0.37
04	1.00	0.90	0.06	0.21	0.37	0.73
05	1.00	0.99	0.08	0.05	0.57	0.91
06	0.99	1.00	0.08	0.02	0.46	0.46
07	0.98	0.88	0.21	0.13	0.68	0.53
08	0.99	0.99	0.06	0.15	0.43	0.95
09	0.95	0.97	0.07	0.20	0.45	0.09
10	0.99	0.98	0.09	0.15	0.88	0.87
Mean	0.97±0.039	0.96±0.041	0.98±0.050	0.18±0.176	0.59±0.194	0.72±0.0.20
P-value	P<0.481		P<0.165		P<0.143	

secured to the table to ensure that the patient is in the correct position during each treatment session. After the CT scan, the images were transferred to the treatment planning system (TPS) to initiate the planning. Table (1.1) shows the mean, max and minimum dose that covered 95% of the target and p-value of the target (PTV) for both modalities. The prescribed dose was 60 Gy.

3.2. PTV

A statistically significant difference between 3DCRT and IMRT and in the mean dose to the PTV ($p < 0.519$) has been observed. The mean value of the PTV was 61.04 ± 1.152in 3DCRT and 60.72 ± 1.005 in IMRT. The maximum dose to the PTV in 3DCRT (64.26 ± 2.36) and in IMRT (62.95 ± 2.33) had a lower maximum dose to the PTV ($p = 0.228$). This result indicates that IMRT was better than 3DCRT. The average minimum dose in IMRT was (46.80 ± 3.89) compared to (49.06 ± 4.98) in 3DCRT, ($p = 0.285$). The dose to 95% of the PTV was (57.73 ± 1.55) in IMRT to (58.20 ± 0.97) in 3DCRT, ($p = 0.423$). Conformity index (CI) was approximately equal in both modalities with an average value of 0.962 ± 0.041 in IMRT compared to (0.969 ± 0.039) in 3DCRT, ($p = 0.481$). The average homogeneity index (HI) in IMRT was 0.187±0.176 and 0.099 ± 0.050 in 3DCRT, ($p = 0.165$). Therefore, IMRT achieved an improvement in HI. Target coverage index (TCI) in IMRT was 0.7213 ± 0.2050 and 0.5970± 0.194 in 3DCRT (Table 1.2).

3.3. Isodose distribution and DVH analysis.

Isodose distributions for the IMRT and 3D-CRT are displayed in figure 1 and 2. The 3DCRT plan contained the PTV receiving greater than 108% of the prescription dose, 65.3 Gy. This was not the case in the IMRT plan, as the dose distribution within the PTV was more homogeneous. There were hot spots (doses greater than 63 Gy) in the lateral portion of the PTV in the 3DCRT plan and in the upper portion of the PTV in the IMRT plan. The distributions showed comparable PTV dose coverage between the two modalities. PTV conformity in the 3DCRT plan appeared worse than in IMRT. The 30 Gy lines extended farther to cover the brain in IMRT than in the 3DCRT plan. However, a small region of PTV in the 3DCRT plan was receiving 65 Gy or greater, the PTV dose conformity was greater in the IMRT

DVH provides useful quantitative dose assessment by direct visual inspection of the dose curve [18]. Figure 3 contains a DVH for the 3DCRT and IMRT plans. The y-axes of a DVH, specifically for the PTV, represent the region where the curve bends away from 100% and "falls off" with the curve maintaining a constant slope. The IMRT plan

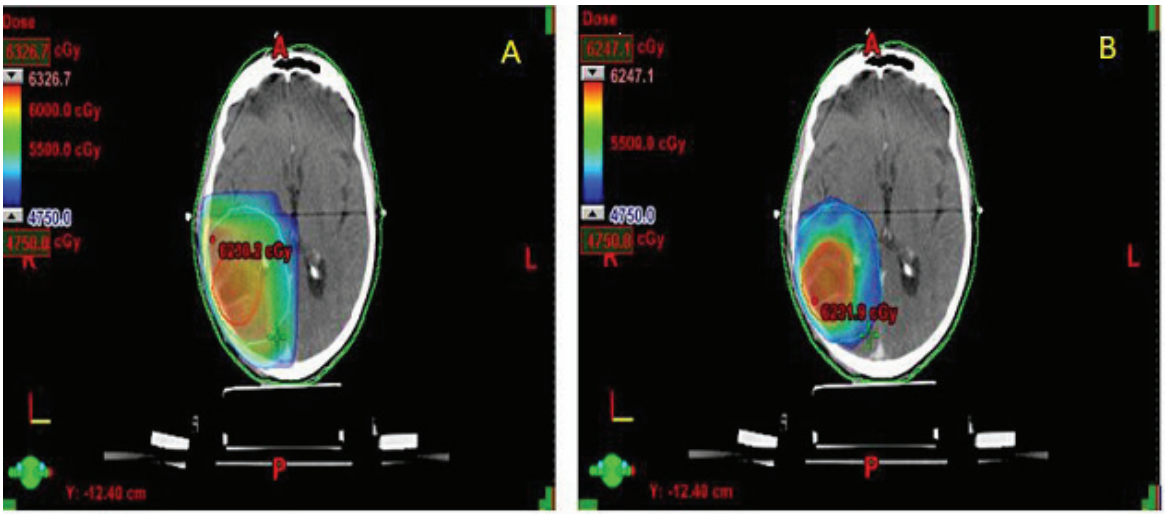

Figure 1: Isodose distribution of patient Rt. parieto-occipital glioma planned with (A) 3DCRT (B) IMRT.

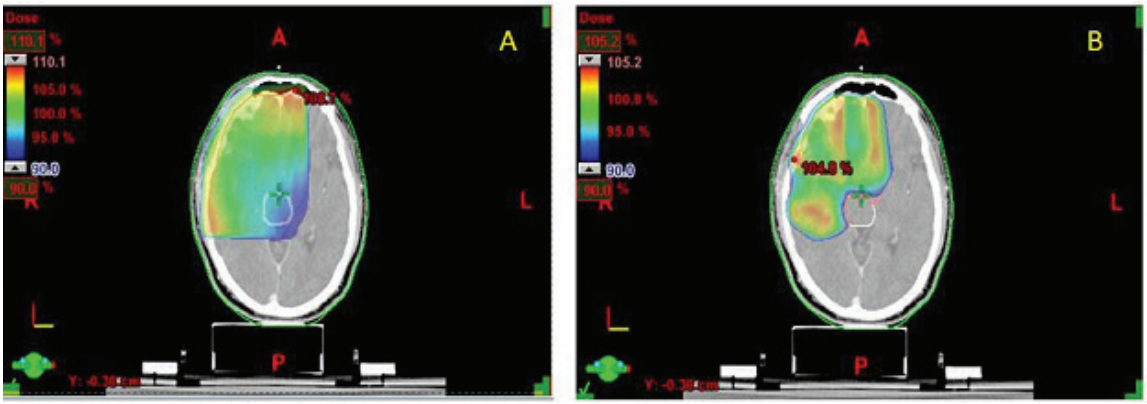

Figure 2: Isodose distribution of patient Rt. parieto-occipital glioma planned with (A) 3DCRT (B) IMRT.

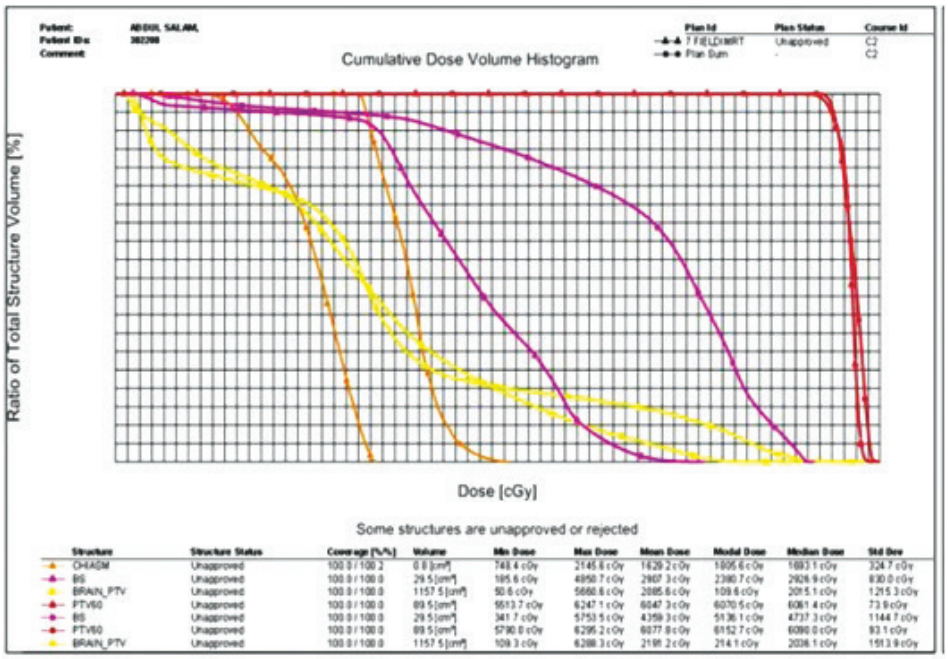

Figure 3: Cumulative dose volume histogram of patient with postoperative malignant glioma in the right parietal lobe glioma. (A) 3DCRT (B) IMRT.

contained a broader region in the PTV, which indicates higher dose coverage compared with 3DCRT. The PTV had a sharper falloff in the IMRT plan representing the superior PTV dose homogeneity observed in the isodose distributions. DVHs showed a low dose to optic chiasm, optic nerve, left and right lens and left eye in the IMRT plan comparable to that of 3DCRT, and also a low dose to the brain stem, spinal cord, right eye and right optic nerve in IMRT.

Discussion

Patients with cerebral malignant gliomas classified as grade III or IV according to the WHO grading system which account for three-fourths of all glioma cases, were included in this study. Surgery is the first choice of treatment, but because of infiltrative growth and no obvious boundaries with the surrounding normal tissue in higher grade malignant glio¬mas, coupled with the peculiarity of the anatom¬ical location, complete surgical resection is often difficult if not impossible. Postoperative radiation therapy has been used as conventional treatment for malignant gliomas with the radiation dose generally being 60 Gy, at 1.8–2.0 Gy per fraction. There has been a dramatic improvement in radiotherapy techniques over the last two decades. Improvements in dose distribution and local control have been observed with 3DCRT as compared with conventional two dimensional treatment planning. It has also been showed that the morbidity of therapy decreased with the use of 3DCRT compared with conventional treatment planning. Furthermore, IMRT has shown improvement in target dose conformity, as well as reduction in the dose to the normal tissues while achieving comparable target coverage when compared with 3DCRT techniques in many treatment sites including esophagus, prostate, paranasal sinuses, nasopharynx and other head and neck sites [1,4,8-11].

In case of treatment of malignant glioma with standard therapy consisting of maximal safe surgical resection followed by involved field radiation therapy and chemotherapy has shown survival advantage in favourable prognostic groups. Uncertainties in target volume definition may not only result in marginal misses of tumor but also in unnecessarily overdosing the normal brain. The recent developments in CNS imaging technology like CT and MRI fusion in radiotherapy planning and functional imaging may further increases the ability to more precisely define the target volume and target the areas at risk of failure. If gliomas can accurately mapped, IMRT may provide further advantage because of its ability to target selected more resistance parts within the tumor with higher radiation doses without increasing the dose to normal tissue. As the number of long term survivors increases, an increase will almost certainly be seen in the number of patients suffering from the late effect of radiation. Therefore to ensure optimal coverage with minimal radiation injury, investigating the integration of advanced, highly conformal radiotherapy techniques for this disease is important. This study was a comparative dosimetric evaluation of IMRT and 3DCRT for treatment of ten patients of malignant glioma, with respect to target coverage, conformity of prescribed dose volume, sparing of organ at risk and integral dose to non-target normal brain tissue.

Comparison of IMRT and 3DCRT for the malignant glioma of the brain are scarce in literature [5,12]. Chan et. al. with a study, group of 5 patients demonstrated that, simultaneous boost in IMRT delivered higher dose to the gross tumor volume while respecting same critical normal tissue constraint and also still maintaining the uninvolved normal brain tissue at dose levels of the 3DCRT . One more study by Narayana et. al. analyzed 20 patients, showed that regardless of tumor location IMRT did not lead to significant improvement in target coverage (maximum dose, minimum dose ,or D95 coverage) when compared to 3DCRT . Our dosimetric analysis confirmed that there was no significant difference in target coverage between IMRT and 3DCRT plans with slight superiority in 3DCRT plan in the range of 95%-100% of prescribed dose. Both techniques were shown good

target coverage in initial PTV and boost PTV. For many gliomas target coverage and dose uniformity are excellent with standard 3DCRT techniques owing to the nearly spherical or cylindrical shape of the lesion. Therefore it was not surprising that significant further improvement was not observed with IMRT. Target coverage and dose uniformity improvement with IMRT have been primarily reported in sights like Head and Neck or Prostate [8, 9], where the target is concave, surrounding normal tissues with dose limits much less than that of the tumor. Gliomas can be highly irregular but typically exhibit few concavities. When concavities do exist such as when the tumors surrounds the chiasm the required dose gradient between tumor and normal tissues is often less than that observed in other sites. As a result very good target coverage is often achieved with 3D planning. However as we

escalate the prescription dose for this tumors even if only to areas of suspected high tumor density, the benefit of IMRT might increase because steeper dose gradients and more concave dose distributions will be necessary. Our study showed almost similar dose uniformity within the target volume both in 3DCRT and IMRT as indicated by high degree of dose uniformity.

Our data are comparable to those reported by Hermanto et. al. where IMRT did not further improve target coverage or dose uniformity within the target, but it did results in statistically significant superiority in target conformity ($p<0.001$), and also significant reduction in the mean and maximum doses to the critical structures like brain stem , optic pathway ($p<0.05$). In IMRT if the normal structures like eloquent cortex, brain stem and optic pathway is located near the target, there is actually a compromise to be done in normal tissue sparing and target coverage in the range of 95%-100% of prescribed dose, because if we optimize stringent dose constraint for normal tissue located nearby target it was trying to create cold spot within the target. Dose received by the 50% of the volume of critical normal tissue was improved in IMRT plans compared to 3DCRT plan. The integral dose was evaluated for Brain-PTV, the average normal brain tissue integral dose was reduced in IMRT compared with 3DCRT by approximately 8%. These finding are comparable with majority of the published studies. A study by Hermanto et. al. [25], demonstrated IMRT decreased the total integral dose to the non-target brain tissue by 7%-10%, Narayana et. al. [23], reported a 7% decrease in mean dose to normal brain with IMRT compared with 3DCRT. In our study, 90% of the patients had absolute reduction of integral dose with IMRT and only about 10% of patient showed high integral dose. The reason for this could be in those cases the tumor was located eccentrically in the occipital lobe and this was adequately covered with two fields with 3DCRT techniques, whereas for the treatment of the same target with IMRT multiple fields at different angulations need to be selected. The passage of beams through larger depth might tend to increase the integral dose to non-target brain. It together underscores the fact that with careful IMRT planning integral dose to the normal tissues can be significantly decreased. With careful planning in regard to choice of beam angles, beam weighting, and recognition of potential exposure of normal tissues to exit dose, our study showed that IMRT enabled improvement in target dose conformity, critical tissue sparing, and reduction of integral dose.

This superior dosimetric advantage of IMRT may prove useful in reducing dose to the surrounding critical structures when tumor is situated very close to these structures, in minimizing the treatment related morbidity like cognition deficit, to improve quality of life and also may have an option to re-irradiate for recurrence of tumor when indicated in long time survivors.

Conclusions

In the present study, target dose coverage was improved with IMRT planning as compared with 3D-CRT planning, and dose to normal structures was concomitantly decreased. With careful planning and judicious selection of beam parameters, IMRT improved target conformity and sparing of critical normal tissues, without increasing the integral dose and low-dose volume in patients with high-grade gliomas. New diagnostic and therapeutic tools hold promise for improving outcomes in patients with high-grade glioma. Combining modern tumor imaging technology with IMRT will permit more accurate tumor definition and radiation dose intensification without increasing injury to normal brain and adjacent critical structures. Moreover, in the era of more effective systemic treatments and an increased number of long-term survivors, the use of IMRT may minimize toxicity and improve quality of life.

Conflict of interest: Nil

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International Journal of Neurology and Neurosurgery	4	11000	10500	859	820
International Journal of Pediatric Nursing	3	6000	5500	469	430
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Case Report

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Aggressive Sebacous Carcinoma of Extremity : A Rare Case Report

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Abstract

Sebaceous carcinoma is an uncommon aggressive malignant tumour derived from the adnexal epithelium of sebaceous gland either from ocular or extraocular sites.

Extraocular sebaceous carcinoma is a rare malignancy when compared to periocular variant. The aggressive types of extraocular sebaceous neoplasm are reported with lymph node and visceral metastasis associated with poor prognosis. Here we report a case of aggressive recurrent extraocular sebaceous cell carcinoma of palm (upper extremity) with recurrence to post op site and ipsilateral axillary lymph node metastasis.[1]

Keywords: Sebaceous Carcinoma, Upper Extremity.

Introduction

Sebaceous carcinoma, first described by Allaire in 1891 accounts for less than 1% of all cutaneous malignancies.[2] Sebaceous carcinoma either be ocular(75%) or extraocular[3] types (25%)[4] Extraocular sebaceous carcinoma has been reported more commonly on the head and neck region[4&5] followed by trunk, salivary glands, genitalia, breast, ear canal and intra oral cavity. Extraocular sebaceous carcinoma involving trunk or extremity is very rare but aggressive malignant tumour arising from sebaceous glands. It is more common in sixth decade of life (mean-63years) with no sex predilection.[6] Which is also evident with our patient reported at the age of 65 years.

Case Report

A 62 year, old male, presented to us with a complaint of swelling over left forearm which was gradually progressive since 5-6 months. On examination there was a single, non tender, well defined and demarcated swelling over subcutaneous plane of ulnar aspect of forearm with no discharge / bleed. His past medical history was unremarkable and there is no family history of similar lesion or any malignancy. Biopsy revealed poorly differentiated carcinoma. Patient then underwent resection with negative surgical margins and histology was inconclusive.

The patient presented after 2 months after resection with complaint of appearance of a nodular swelling 5 x 3 cm, skin coloured, hard without any signs of

inflammation over skin of left axillary region and ipsilateral axillary lymph node metastasis (fig 1). A subcutaneous soft tissue nodular lesion 3 x 2 cm on lateral aspect of palmar region, left hand and two other soft tissue lesion 1 x 1 cm at anterolateral aspect of left 4th metacarpophalangeal joint. Patient underwent amputation of left forearm along with left axillary lymph node dissection (fig 2). The frozen section revealed skin adnexal carcinoma with involvement of medical resection margin shows tumour deposits. In frozen section, tumour composed of round to polygonal cells with high N:C ratio, hyperchromatic nuclei, scanty to moderate cytoplasm; forming lobules, cords and acini, infiltrating subcutaneous tissue (fig 3). The postoperative course was uneventful. The analysis of surgical specimen revealed sebaceous carcinoma (Grade 2) (fig 4). Left hand with metastasis to left axillary lymph node with extra nodal extension (pT4 N1b Mx). Tumour infiltrating overlying skin with ulceration LVE +, PNI +, left axillary matted lymph node level 1 and 2 show metastasis with extra nodal extension. Left axillary level 2 lymph node (2/18) showed tumour metastasis. Patient was planned for 1 cycle neoadjuvant chemo with Paclitaxel and Carboplatin followed by EBRT to axilla and then to continue chemo with Paclitaxel and Carboplatin but patient delayed the treatment and reported after 1 and 1/2 month of amputation, to us with multiple tiny nodules over flexor aspect of amputated (fig 7) left forearm (cutaneous metastasis) then he was planned for EBRT to axilla by photons and EBRT to forearm by electron followed by chemotherapy. Patient was taken to mould room for preparation of mould (fig 5) to ensure immobilization during the course of treatment. After CT simulation with proper immobilization technique, treatment plan was generated with contoured target volumes and organ at risk. (Fig 6) He was planned for a prescription dose of 54 Gy/30# (@1.8 Gy/#) to left axilla and 60 Gy/30# (@ 2 Gy/#) to arm using 6 MV photon on DMX Varian Linear accelerator. He tolerated the treatment well. (fig 8) And is now being treated with chemotherapy with Paclitaxel and carboplatin.

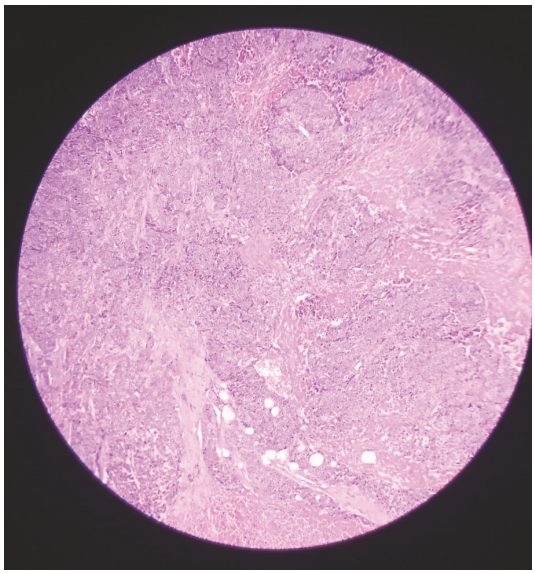

Fig 1 : Frozen Section Histopathology Image

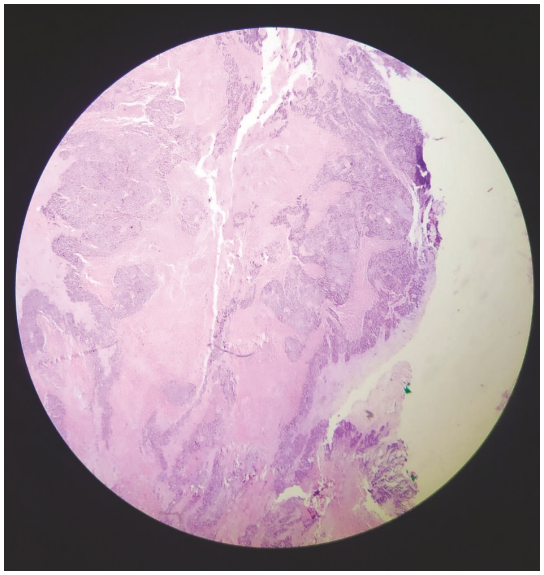

Fig 2 : Post Op Histopathology Image

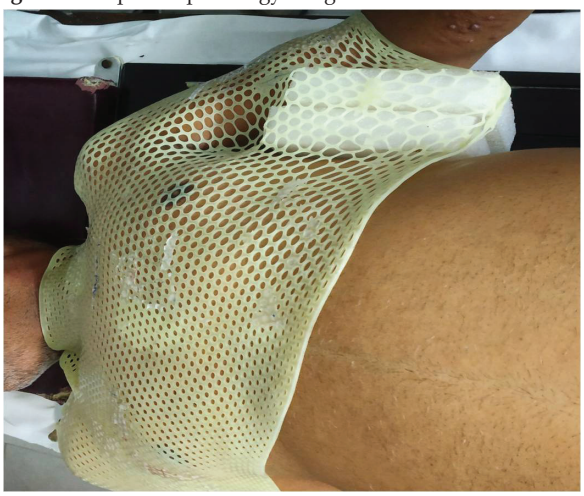

Fig 3 : Mould Preparation

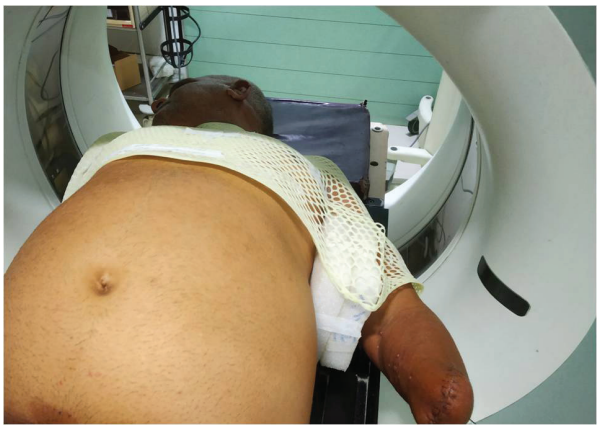

Fig 4 : CT Simulation

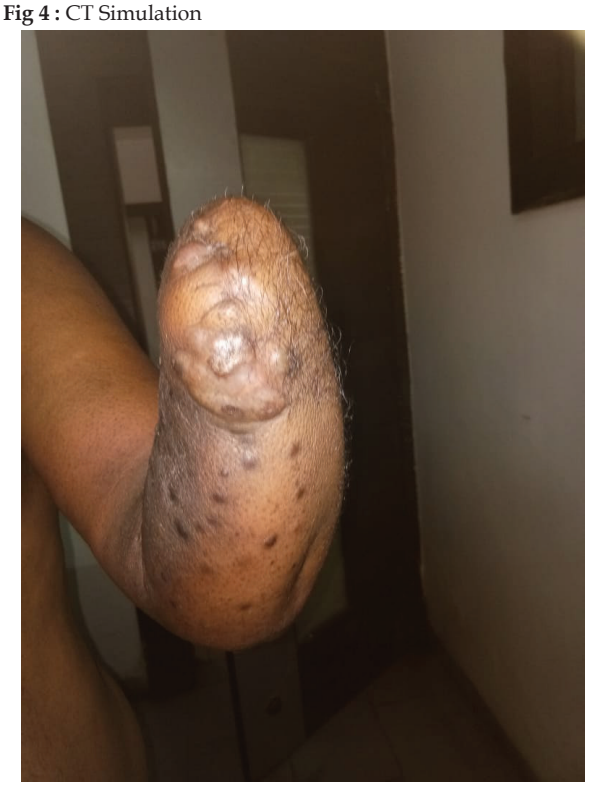

Fig 5 : Image of Amputated arm During Course of Radiotherapy

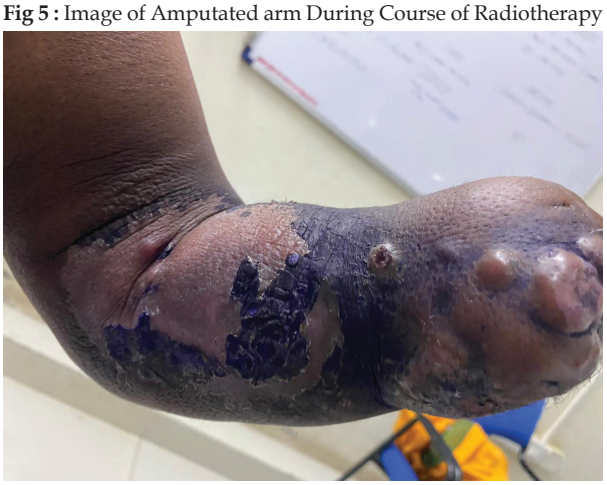

Fig 6: Image of Amputated arm After Completion of Radiotherapy

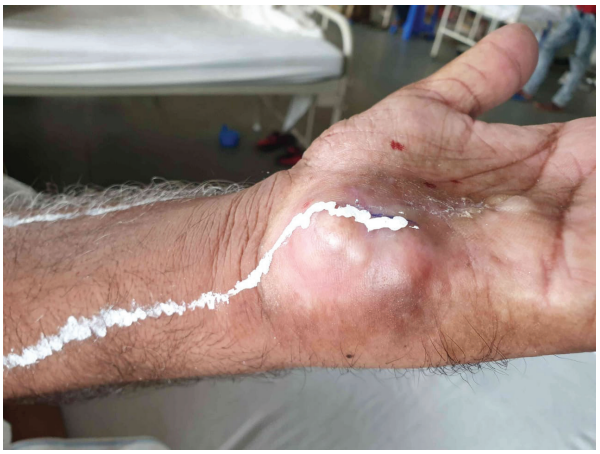

Fig 7 : Nodular Swelling Lt hand Before Excision

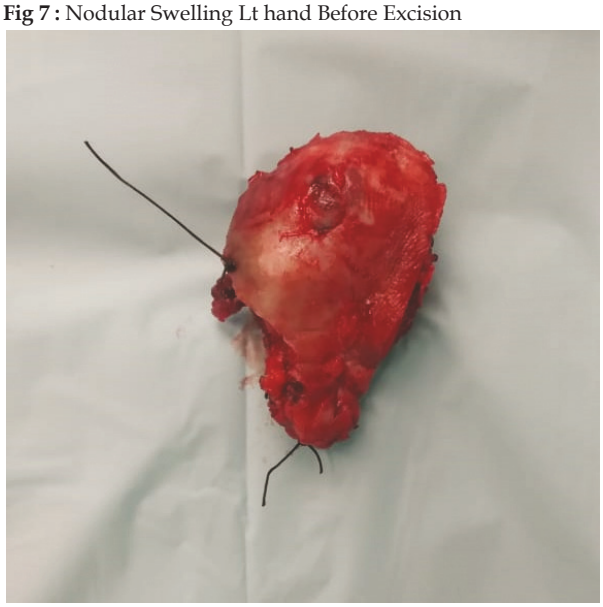

Fig 8 : Nodular Excised Tumor

Discussion

Extra ocular sebaceous carcinoma involving the extremity is very uncommon, aggressive malignant tumor arising from sebaceous glands. Mean age of occurrence is 63 years involving both sexes in equal proportion. The disease exhibits a variety of histologic growth patterns and diverse clinical presentation that diagnosis is often delayed for months to years.[7] The most frequent clinical presentation is a painless subcutaneous firm nodules (79%) located in dermis or hypodermics of variable size (0.5to 5cm). Our patient reported to us with a similar presentation of painless swelling. Sebaceous carcinoma of extremity can also present as pedunculated lesions, irregular mass or diffuse thickening of skin. This protean appearance frequently masquerades as other benign tumours or inflammatory conditions, thereby leading to delay

in diagnosis, inappropriate treatment, increased morbidity and mortality. The lesions usually present as pink to red yellow nodular growth in skin and may clinically resemble pyogenic granuloma, haemangioma or squamous cell carcinoma. The draining lymph nodes may be involved in few cases only like in our case.

Regardless of the location, this malignancy is highly aggressive with a potential for regional and distant metastasis. Our patient also presented with recurrence of multiple cutaneous nodules at post op site along with ipsilateral axillary lymph node metastasis although there was neither distant metastasis nor any sign of internal visceral malignancy.

Sebaceous carcinoma histologically may be classified as well, moderately or poorly differentiated. The morphological hallmark of sebaceous differentiation is the detection of sebaceous cells and demonstration of fat in vacuolated tumour cells. Other differential diagnosis includes basal cell carcinoma with sebaceous differentiation for poorly differentiated sebaceous cell carcinoma. Basal cell carcinoma exhibit peripheral palisading and clefting from the adjacent stroma.

Sebaceous carcinoma express immunohistochemical markers such as cytokeratin, epithelial membrane antigen(EMA), Cam 5.2 and anti breast carcinoma associated antigen-225 antibody.

The common associations of sebaceous carcinoma are Muir-Torre syndrome; an autosomal dominant condition comprising of sebaceous neoplasm with one or more low grade visceral malignancies and Nevus sebaceous of Jadassohn[8] in the absence of other participating factors such as radiotherapy and AIDS.[9]

Distant metastasis and recurrence rates are more common in the ocular type of sebaceous carcinoma [3,10] when compared to extraocular sebaceous carcinoma.

Treatment of sebaceous carcinoma requires wide local excision with removal of involved regional lymph nodes. But Nelson showed that the chances of local recurrence are very high as seen in our patient also.[11] Bailet reported a review of 92 patients with extraocular sebaceous carcinoma and found a recurrence rate of 28% and metastasis in 21% of cases after local excision.[12] Bhandari V[13] also reported a case report of sebaceous carcinoma focussing on its aggressive nature where limited response was seen after chemotherapy. Radiotherapy has been considered as an adjunctive or palliative treatment but is generally not recommended as a primary treatment. The role of chemotherapy has not been defined due to scarcity of these lesion

Conclusion

Extraocular sebaceous carcinoma is a rare malignancy; the arm localisation is even rarer. This is an uncommon but aggressive malignant tumour with higher incidence of recurrence and distant metastasis. The diagnosis is essentially histological; the treatment of choice is radical surgery. More diagnosed is early and more the surgery is extensive more the prognosis is better. Regular follow up is necessary to detect local recurrence, locoregional or metastatic spread.

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Case Report

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Extra Corporeal Irradiation to Treat Osteosarcoma at a Tertiary care Institute in Central India: A Case Report

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Abstract

Extra corporeal irradiation (ECI) is a rarely employed technique of irradiation in malignant bone tumour. In this procedure post en-bloc resection of bone it is irradiated with a dose of 50Gy in a single fraction and then it is reimplanted. This procedure ensures high rate of local control, better anatomical fit and functional outcome. In this case report we present the first case of extracorporeal irradiation in central India.

Keywords: Extra corporeal irradiation, malignant bone tumour, osteosarcoma.

Introduction

Malignant primary bone tumours are relatively a rareentity. These are most commonly seen in children and adolescent.[1] The incidence of osteosarcoma cases are 4-5 per 1000000.[2-5]

The treatment of osteosarcoma requires multimodality approach for optimal management, requiring expertise of surgical oncologist, radiation oncologist, medical oncologist. The management of malignant bone tumours (MBT) have undergone immense advancement in last two decades. During the initial days of oncology, the preferred treatment of MBT was surgical resection (amputation). A shift in treatment strategy was developed with the aim of limb salvage. This treatment modality for limb preservation aims at better local control of the tumour and reconstruction of the limb which wouldresult in restoration of organ function leading to better quality of life and an improved survival.

The principle we follow here, firstly we do en-bloc resection of the involved segment of the bone. After which removal of all the grossly and macroscopically present tumour over the bone segmentfollowed by extracorporeal irradiation (ECI) of the bone segment to achieve maximumtumoricidal effectalong with sterilization and then re-implantation of the bone into the body. ECI achieves maximum tumour kill and also sterilizes the bone. Some of the techniques employed for sterilisation of bone before re-implanting it areautoclaving, microwave, pasteurizing, liquid nitrogen, and radiotherapy (extracorporeal radiotherapy).[6-10] With ECI we deliver a very high dose of radiation (50-300 Gy) in single fraction which results in maximum tumoricidal effect. With this case report we tried to analyse the potential benefits and limitations faced during implementation of ECI at our institute.

Case Report

A 38-year-old, female, presented to us with initial complaint of swelling over lower end right thigh since 3 years. It was gradually progressive in

nature with no complaint of pain over the swelling initially. She had no difficulty in limb movement in the beginning. Eventually she started to experience pain while sitting in cross legged position since 2 years. On local examination there was a swelling over the lower third of right thigh involving the anterio-lateral region of the thigh. Swelling was around 12 × 15 cms, well-defined margins, hard, fixed, non-tender. No popliteal lymph nodes or inguinal lymph nodes were found on palpation. Initial x-ray showed a large mass over her right distal end of femur. (figure 1). MRI distal knee joint suggestive of large mass lesion with soft tissue and calcific component seen in distal thigh arising from cortex of metaphyseal region of distal femur posteriorly and posterior-laterally. No surrounding marrow oedema or extension of lesion into medullary cavity. No significant infiltration of lesion into adjacent muscles which are displaced peripherally by lesion. Increased fluid seen in suprapatellar bursa. Findings suggestive of malignancy? Paraosteal osteosarcoma. Biopsy from the right thigh swelling suggestive of conventional osteosarcoma. Her CT scan chest was suggestive of few sub centimetric nodules in bilateral lung bases. The patient also underwent whole body scintigraphy scan which was suggestive of increased uptake of distal end of right femur. And no other evidence of distal skeletal metastasis. Her biopsy block review reported parosteal osteosarcoma (figure 2).

The patient did not seek any medical care and reported five months later to us. After a full routine and metastatic work up which revealed no evidence for lung metastasis or distant metastasis? She was started with neoadjuvant chemotherapy plan according to OGS-12 protocol. Received four cycles of neoadjuvant chemotherapy, first two cycles with cisplatin and doxorubicin for three days and then she was switched to ifosfamide and doxorubicin for three days for next two cycles.Post completion of her neoadjuvant chemotherapy her CT scan Right lower limb (figure 3) was suggestive of space occupying lesion of size 10.4 × 8 × 12 cms in the distal portion of right thigh arising from the right posterolateral parosteal aspect of femur showing areas of dense bony calcification mingled with soft tissue component.No obvious intramedullary component. The lesion is 1.5 cms proximal from the knee joint. The goal behind multi-disciplinary treatment approach at our institute is the best treatment for the patient utilising all the speciality. The patient post chemo was referred foronco-surgery and radiation oncology opinion where she was planned for wide local excision along with extra corporeal irradiation.

For extra corporeal irradiation the involved segment of bone was excised, all the grossly involved tumour over the bone was removed (figure 4), in order prevent contamination it was then transferred to a different sterile tray over a different trolley where at first it cleaned with normal saline, all the bone marrow present in the excised section was removed using suction and thenwrapped with a layer sterile wet drape soaked with 2 gm of vancomycin (figure 5) and then another two-layer surgical plastic packing. The thickness of wrapping around the bonesegment was of 3cm. The wrapping ensured no air gaps were left and would help in achieving homogenous dose distribution. The 3 cm of layeredwrappinghelped us achieve the 'build-up' effect to the bone. The sealed segment of bonewas transferred to Computed tomography (CT) console for imaging and then the images were transferred to treatment planning system (TPS). Eclipse version 13.7 (Varian medical Systems Pvt. Ltd., Palo Alto, CA, USA), where CTV and PTV were contoured. Plan was generated. Bone was shifted to Medical Linear Accelerator Clinac DMX (Varian Medical Systems Pvt.Ltd.,Palo Alto, CA, USA) treatment couch ensuring proper immobilization. 2 D treatment was planned. Plan was approved in two parts of 25 Gy each since a single fraction plan of 50Gy was difficult to approve.Matching was seen with beam light and source to surface distance (SSD) was checked just like cobalt. The appropriate field size for radiation treatment was selected making sure it covered the entire segment of bone. A single fraction dose of 50 Gy using 6 MV photons was delivered in two parts to the mid plane of bone segment using a parallel-opposed anterio-posterior and posterio-anterior fields. Treatment time for each part was 10minutes. Treatment was done on service mode and not on routine mode. After completion treatment delivery the bone segment was returned to operation theatre maintaining proper chain of aseptic precaution without any delay. The total time required was almost 40 minutes in which radiation delivery time was 20minutes and the rest of the 20 minutes in shifting of bone segment, imaging and planning. Post ECI biopsy samples were taken from various sites of the bone which turned out negative for presence of malignancy (figure 6). Post ECI the bone segment was pale and lost all its tumour which present after resection (figure7). The bone was autoclaved and then re-implanted into the body. And post procedure x-ray done. (figure 8) The patient started to weight bearing over her lower limb with support on post procedure day 7 and there after ambulation with support began post procedure day 15. Patient is on regular follow up

walking comfortably with support. Follow up to continue every 3 monthly for two years.

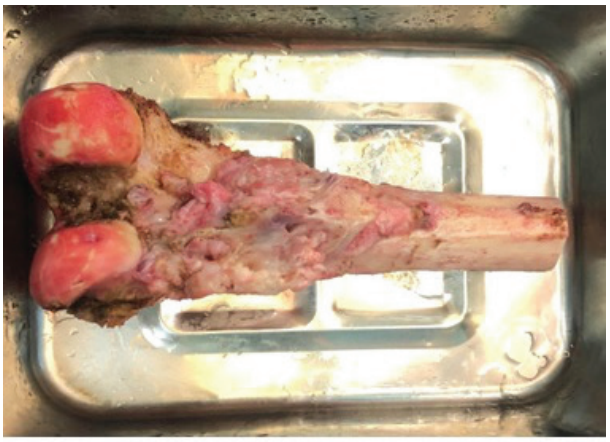

Fig 1. Post Resection Femur with Residual Tumor

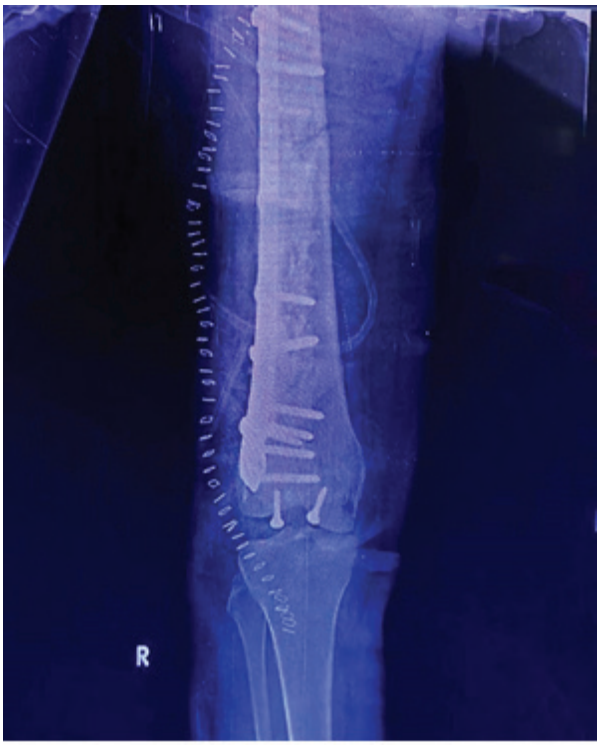

Fig 2. Post Fixation X-Ray

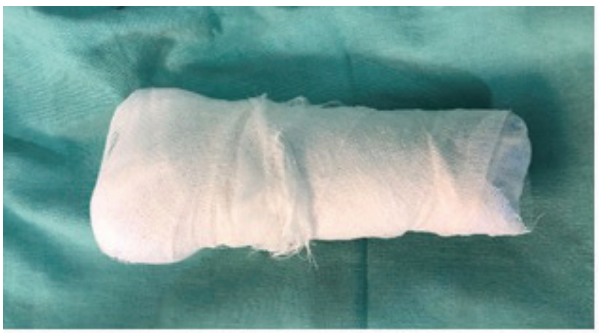

Fig 3. Layered Wrapping of Bone Segment for Radiation

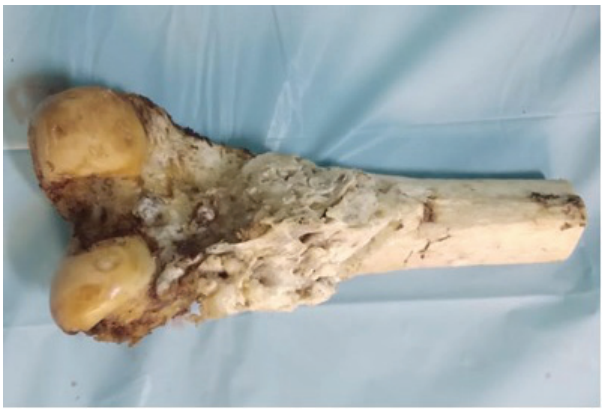

Fig 4. Post ECI Bone Segment

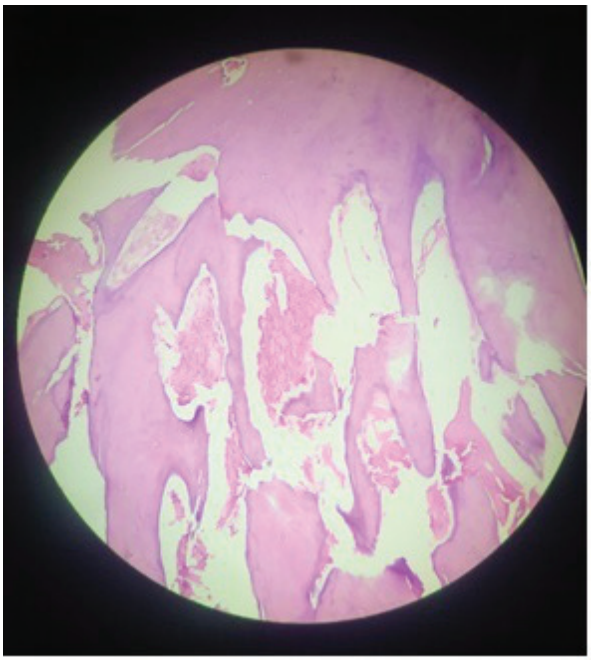

Fig 5. Post ECI Biopsy Showing no Active Cells

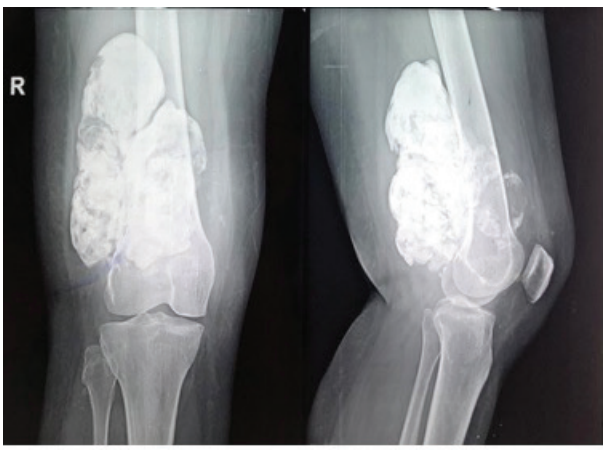

Fig 6. Pre op CT scan

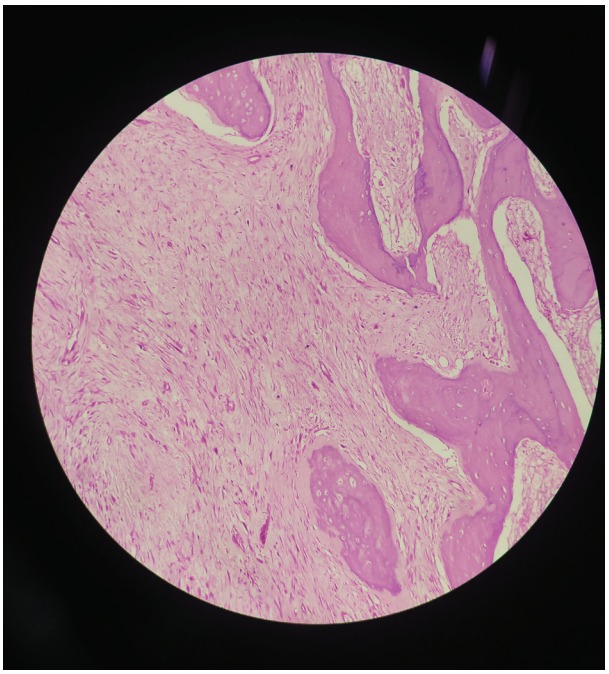

Fig 7. Histopathology

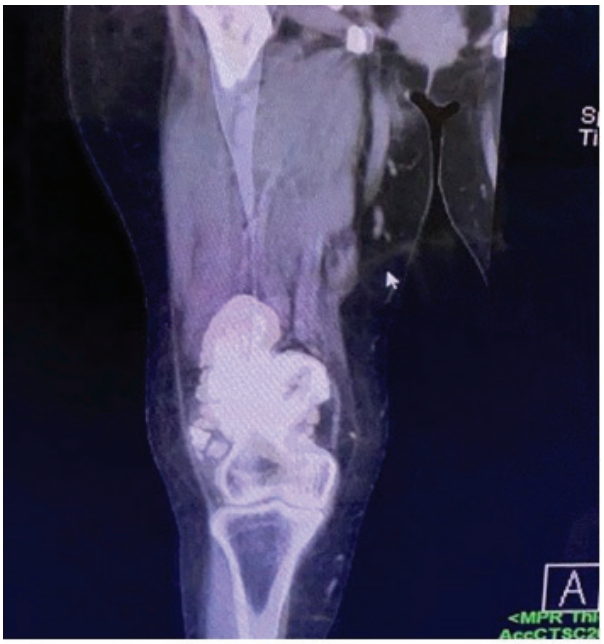

Fig 8. Pre Op X-ray Distal end Femur

Discussion

The entire appeal of multi-modality approach lies in providing the best care utilising all the faculties of oncology and to achieve the best outcome for the patient. In MBT limb preservation could lead to a better quality of life. One of the key requisites of delivering ECI is the availability of all the modalities at one institute. The need of proper operating room, CT scanmachine for imaging, and the linear accelerator to deliver radiation at one centre in close proximity is of utmost importance since time management is very crucial while executing ECI. Limb salvage would result in better quality of life and functional outcomes for the patient. Limb reconstruction can be done using artificial prosthesis, allografts and autografts. Allografts which are biologically reconstructed[11] require access to large bone banks and to find a matching bone donor and immunogenicity is difficult, and also expensive. This also arises concerns regarding the increased chances of transmission of infections from allografts. So, the role of ECI hold simmense importance in utilizing patients' own bone segment (autograft) as it provides a perfect anatomical fit, high dose of radiation ensures tumour kill, convenient, cost effective and also minimizes the risk of any disease transmission. Recycled irradiated autograft was first reported by Spira and Lubin in 1968.[12] Before re-implanting the bone segment into body bone sterilisation is a must. One of the advantages that we see with ECI is limb function preservation which translates into weight bearing and ambulation.In a study conducted by Uyttendaele et,[13] 15 patients with primary malignant bone tumours were treated with ECI and they were followed up for 5 years and showed excellent weight bearing. Similar studies were conducted Hong et al,[14] and Chen et al,[15] exploring the potential advantages of ECI and autograft implantation. With ECI very high radiation dose (50-300Gy) can be delivered. We delivered ECI with 50Gy in a single fraction since previous studies which states no added benefit with increase in dose and states chances of detrimental effect of with higher doses of radiation.[16,17,19] The advantages with delivery of such high dose is the maximum tumoricidal effect can be achieved which minimizes the chances of local recurrence which was also evident in a study conducted by Poffyn et al,[18] where they had 0% recurrence post treatment with ECI. And another study conducted by Davidson et al[19], with 50 patients where 4 patients had recurrences. Most of the studies that we have been conducted with ECI for MBT had a heterogenous group of primary malignancy which makes it hard to conclude if the recurrence was due to tumour biology or due to failure of ECI.[1,12,13, 14, 15,18] The dose rate for ECI is still a matter of discussion and area that needs to be explored. Though, with ECI we can deliver doses without any radiation related toxicity to the normal tissue since the bone has been removed from the body. There is no chances of unnecessary radiation exposure to surrounding

structures. In study conducted by Ahmad fauzi et al[20] comparing various methods of limb salvage ECI was found to be good and convenient option. ECI can only be executed successfully in patients where biomechanical properties of the bone segment are intact.

The potential benefits of the procedure and a few limitations faced during the procedure as summarised in the table below:

Benefits	Limitations
Higher local tumour control	Single Plan approval could not be done due to high prescription dose.
Minimal chances of recurrence	Time is limiting factor since the bone is to be irradiated and transported back into the OT within a limited interval.
No dose related normal tissue toxicity	Technically feasible set up is needed to execute the treatment.
Anatomically perfect fit with autografts	To draw conclusion between local tumour control and overall survival large scale study with a higher sample size needs to be done.
No requirement of finding a matching donor bone and immunogenicity	Chances of graft failure
No need to have an access to bone banks	Perioperative complication
Cost effective	Delayed healing of wound.

Conclusion

ECI and autograft reconstruction procedures for limb salvage are good, cost effective, and convenient treatment option with good anatomical and functional outcome. The relation between overall survival and local tumour control needs to be studied since most of the studies in literature had a small sample size. Further studies with a much larger patient cohort. The radiation delivery requires prior preparation to be carried successfully within limited time frame. This technique when employed with proper selection of patient could do wonders in regards to local control and post procedure life style of patient.

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[2] Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, *et. al*. Caries-preventive effect of fluoride toothpaste: A systematic review. Acta Odontol Scand 2003; 61: 347–55.

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[4] American Academy of Periodontology. Sonic and ultrasonic scalers in periodontics. J Periodontol 2000; 71: 1792–801.

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[6] Hosmer D, Lemeshow S. Applied logistic regression, 2nd edn. New York: Wiley-Interscience; 2000.

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[7] Nauntofte B, Tenovuo J, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O,

Kidd EAM, editors. Dental caries: The disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. pp 7–27.

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[8] World Health Organization. Oral health surveys - basic methods, 4th edn. Geneva: World Health Organization; 1997.

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