Original paper

High-dose-rate interstitial brachytherapy in recurrent head and neck cancer: an effective salvage option

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Abstract

Purpose: High-dose-rate (HDR) interstitial brachytherapy has an established role in head and neck malignancies and offers good survival rates; however, there is scant data on improved local control (LC) and treatment-related complications in recurrent cases. We present our results in patients with recurrent head and neck cancers treated with HDR interstitial brachytherapy.

Material and methods: Twenty-five patients with recurrent head and neck cancers were treated with HDR interstitial brachytherapy using Iridium 192 between 2009 and 2016. Of these, 75% received radical brachytherapy, and 25% received external beam radiation therapy (EBRT) followed by brachytherapy boost. Treatment sites included oral cavity (15/25) and oropharynx (10/25). Median dose of 4.5 Gy was administered twice per day, with median total brachytherapy dose of 40.5 Gy in radical and 27 Gy for EBRT cases.

Results: With median follow-up of 25 months, 4 local recurrences were observed within first year of follow-up. Two-year local control and overall survival outcomes for the entire group were 75% and 68%, respectively. Local control rate with radical BRT vs. BRT as a boost following EBRT was found to be significant (2-year LCR 62% vs. 85%; $p < 0.02$). Dosimetric assessment revealed D_{90} – 4.08 Gy, V_{100} – 94.1%, V_{150} – 24.7%, and V_{200} – 10.1%. Xerostomia, altered taste, and dysphagia were the major complications commonly grade 1 and 2. Grade 3 toxicity was only 2%. Pre-treatment volume > 85 cc had a negative impact on overall survival (26 months vs. 12 months; $p = 0.02$), and interval time between primary and recurrence more than 15 months had an impact on the local control rate ($p < 0.01$).

Conclusions: Results of HDR interstitial brachytherapy have shown acceptable local control and overall survival rates along with tolerable toxicities and morbidity in recurrent head and neck cancers.

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Key words: HDR brachytherapy, head and neck cancer, recurrent tumor.

Purpose

Head and neck malignancy management has seen many advancements; nevertheless, approximately 20-50% of patients are diagnosed with loco-regional recurrence within first two years [1,2]. Surgery forms the major treatment modality but can be possible in only 20% patients, leading to overall 5-year survival of 20% to 30% [3,4,5,6,7]. External beam radiation therapy (EBRT) can lead to severe local toxicities in view of reirradiation to the primary. High-dose-rate brachytherapy (HDR-BRT) however, can deliver a high dose directly to the target volume, and provides the advantage of rapid dose fall-off, thereby allowing for sparing of normal tissue [8,9,10].

With the advent of 3DCRT (3D conformal radiation therapy) and IMRT (intensity modulated radiation therapy), as more conformal treatment techniques, there has been a rise in the publications presenting results with the use of these treatment techniques, demonstrating the survival outcomes and toxicity profiles associated with reirradiation in head and neck malignancies. However, in most cases, even these techniques cannot prevent the dose fall off to the surrounding normal tissue, thus leading to acute and late toxicities, and sometimes even compromising the doses to target volumes itself leading to future recurrences and failures.

High-dose-rate brachytherapy offers significant advantages over conventional LDR (low-dose-rate) brachy-

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therapy by reducing concerns of radiation safety for the staff during hospitalization and provides the clinician with a greater control over the dose distribution by using computer optimized dwell times within the individual catheters. With HDR-BRT, dosimetrically equivalent or superior outcomes compared to LDR brachytherapy and EBRT for gynecological tumors and other locations have been achieved [11,12]. However, the same data in head and neck malignancies and the use of interstitial brachytherapy is minimal. In this study, we present our results and experience with retrospective analysis demonstrating our recent experience in the use of HDR-BRT in management of recurrent head and neck malignancies.

Material and methods

Patient characteristics

From January 2009 to June 2016, twenty-five patients with histopathologically proven recurrent head and neck malignancies were treated with HDR-BRT at Jupiter Hospital, Thane, India. The primary treatment characteristics and patient characteristics are shown in Table 1. Most of the patients had recurrence in the region of previous EBRT or surgery. Out of these 25 patients, 10 were recurrences in oral cavity and 15 in the oropharynx. The patients were evaluated for surgery and found to be ineligible for varied reasons, therefore chosen for radiation therapy with HDR-BRT. There were 14 males and 11 females who underwent reirradiation with HDR-BRT. The median age of these patients was 57 years (range: 34-76 years). In view of larger primary tumors, the patients underwent external beam radiation first, followed by brachytherapy boost. Thus, the study consisted of 18 patients who underwent radical BRT and 7 patients who underwent brachytherapy boost following EBRT. The treatment characteristics are shown in Table 2.

Table 1. Primary treatment characteristics

Parameters	No.
Primary treatment	
Surgery alone	11
Surgery + EBRT	14
Radiation dose	Median 66 Gy
Time to relapse	Median 15 months (3-40)
Gender	
Male	14
Female	11
Median age (range)	57 (34-76)
Implant location	
Oral cavity	10
Oropharynx	15
Treatment modality	
Radical brachytherapy	18
EBRT with BRT	7

EBRT – external beam radiation therapy; BRT – brachytherapy

Brachytherapy

The implant procedure was performed under general anesthesia. A nasogastric tube was placed for feeding during treatment. A straight stainless-steel needle was introduced through the sub-mental skin with respect to the site and traversed through the floor of mouth or implanting organ, exited at the other end of operative bed. Subsequent needles passed next to the first one as needed with respect to number of lines and planes, in order to keep interval distance of 14-16 mm between them, according to the need to cover the target. A plastic catheter was threaded through each needle and then, the needle was removed, leaving the catheter in place. The number of catheters varied according to the dimension of the target (Figure 1). The plastic catheters were placed in the operative bed as near parallel as possible at 14 to 16 mm intervals, taking care of peripheral fall-off with a security margin of 10 mm in all directions around the target, using modified technique. The catheters were held to the skin exit points with plastic buttons [13,14]. This implantation technique was used for the various HNC sites.

Prophylactic tracheostomy was not done routinely, except for one patient, where lingual surface of epiglottis was involved. After implantation, all patients underwent a computed tomography (CT) scan, with a slice thickness of 3 mm for three-dimensional (3D) treatment planning. Intravenous contrast was used when necessary to visualize the carotid vessels. The CT study was transferred to the Flexiplan system (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). PTV (planning target volume) and OAR (organ at risk) were contoured and catheters were reconstructed. The treatment planning process was done by computer-assisted dose optimization (Figure 1). The prescribed dose was in the range of 3.5-4.5 Gy per fraction, depending on the site and status

Table 2. Treatment characteristics

Parameters	Total patient n = 25
Median number of fractions	10 (6-12)
Brachytherapy radiation dose	
Radical (median)	40.5 Gy
With EBRT	27 Gy
Implant volume (median)	85 cc (38-270 cc)
Median follow-up	25 months
Grade of differentiation	
Well	3
Moderate	9
Poor	13

EBRT – external beam radiation therapy

of the disease. Fractions were given twice a day with 6 hours apart (median: 10 fractions). The dose parameters were assessed through DVH (dose volume histogram) in percentage. Prescribed and reported doses were specified by D_{90} (dose received by 90% of the volume), as determined by DVH. The implant was planned after 2-3 weeks of completion of EBRT. In cases where BRT was used as a boost, median gap between external and implant was 21 days.

The implant tubes were removed after planned BRT doses were delivered. Total dose (EBRT/BRT) was kept within tolerance levels and has been assessed by estimating biologically equivalent doses (BED) [8,9]. The median dose with radical BRT was 40.5 Gy, and the dose with BRT boost was 27 Gy. The median dose to primary target volume with EBRT was 50 Gy (range: 46-50 Gy). The median implant volume was 85 cc (range: 38-240 cc). Overall, the median number of fractions were 10 (range: 6-12).

Follow-up

Patients underwent follow-up evaluation at every 4 weeks for the first 6 months, every 3 months for the next 6 months, every 6 months for the next 3 years, and annually thereafter. Biopsy was avoided unless it was essential to confirm residual/re-recurrent disease. Overall, follow-up ranged from 8 to 50 months (median: 25 months) for all patients. Twenty patients reached the two-year follow-up and of these, 6 patients reached the five-year follow-up; these patients were alive at the time of reporting in December 2017. The patients were followed-up with routine investigations including complete blood counts, chest X-ray, and ultrasonography of the neck. In suspicious cases, CT of the neck was done.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (Statistical Package for Social Sciences 17.0 for Windows) statistical software. Survival results were calculated using the Kaplan-Meier method and log-rank test. The time origin was the date of the first HDR-BRT procedure. The endpoint of overall survival (OS) was death from any cause. The endpoint of disease-free survival (DFS) was any type of recurrence (e.g., failure at the primary site or regional lymph nodes, distant metastasis). The endpoint of interest from local control (LC) was defined as tumor regrowth in the treated area with BRT or in an adjacent region (e.g., failure at the primary site or regional lymph nodes). The patient DFS and OS were calculated from the last date of their follow-up. Toxicity assessment was done using the RTOG toxicity assessment scale, and late toxicities were defined as features persisting or occurring beyond 90 days.

Results

Overall survival

The median survival calculated for patients who underwent reirradiation with HDR-BRT at 1- and 2-year overall survival was found to be 77% and 68%, respectively. The median follow-up was 25 months. There was a difference in the survival rates in radical versus boost arm as shown in Figure 2.

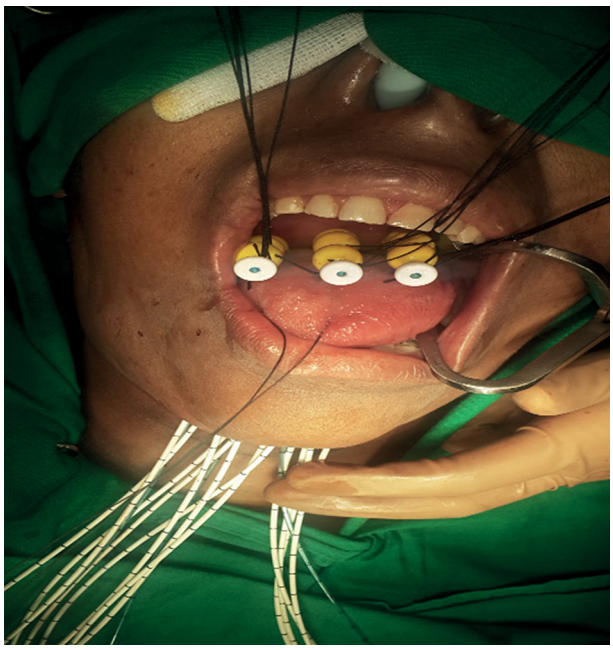

Fig. 1. Plastic bead placement using Bhalavat's technique for interstitial brachytherapy

Local control

The local control rates calculated at 1- and 2-year follow-up were found to be 84% and 75%, respectively. The median time to development of recurrence was found to be 9 months, and was found to be seen more with a larger tumor implant (CTV > 85 cc) and more common in the EBRT + BRT arm. The local control rate with radical BRT vs. BRT as boost following EBRT was found to be significant (2-year LCR 62% vs. 85%; $p < 0.02$). Similarly, the disease specific survival was found to be 74% and 67%, respectively, at 1- and 2-year follow-up.

Toxicity

The late toxicities were assessed as per the Radiation Therapy Oncology Group (RTOG) scale on each follow-up of the patient, and late toxicities were defined

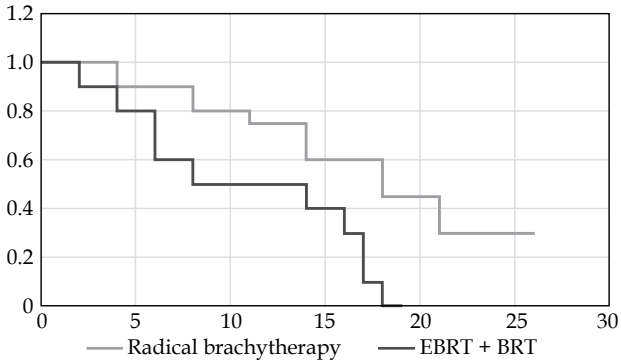

Fig. 2. Survival analysis between radical brachytherapy versus brachytherapy as a boost

Table 3. Assessment of late toxicities

Toxicity parameter	Grade 1	Grade 2	Grade 3	Grade 4
Xerostomia	12%	4%	0	0
Taste alteration	25%	12%	2%	0
Dysphagia	8%	3%	0	0
Delayed wound healing	0	0	0	0
Persistent hoarseness	3%	0	0	0
Fibrosis	5%	3%	0	0

as those occurring beyond 90 days. Most of the toxicities noted were grade 1 or 2 and only 2% grade 3 toxicity were noted in the form of taste alteration. No grade 4 toxicities were noted among the patients. Taste alteration (grade 1 and 2, 25% and 12%) and xerostomia (grade 1 and 2, 12% and 4%) were the common toxicities noted. Other significant toxicities noted were dysphagia (grade 1 and 2, 8% and 3%), persistent hoarseness (grade 1 and 2, 3% and 0%), and fibrosis (grade 1 and 2, 5% and 3%). As compared to other studies, there was no incidence of delayed wound healing, cranial nerve palsy, and osteoradionecrosis associated with brachytherapy procedure noted in our study. The cumulative incidence of grade 1 and 2 toxicities at 2-years were 12% and 8%, respectively (Table 3).

Prognostic factors

A univariate Cox analysis on the significant prognostic factors affecting the survival outcomes was performed, including N stage, dose of first irradiation, interval between the two treatments, and implant volume. Pre-treatment volume of 85 cc was found to be significant for favorable overall survival. The overall survival was found to be 26 months and 12 months (p = 0.02), respectively, for implant volume less than and more than 85 cc. Time interval since last treatment was found to be significant for the better local control rates. For interval of less than 15 months, the local control rate was for 10 months as opposed to 31 months in patients who had a treatment interval of more than 15 months (p < 0.01). As expected, lower nodal status disease had better overall survival outcomes (N0-1 vs. N2-3; p = 0.025). The results are depicted in Figure 3.

Dosimetric outcomes

On dosimetric assessment, the dose parameters were evaluated, and optimization assessed. Dose heterogeneity was specified by V_{100} (the percentage of implant volume receiving 100% of the prescribed dose), V_{150} (the percentage of implant volume receiving 150% of the prescribed dose), and V_{200} (the percentage of implant volume receiving 200% of the prescribed dose). In our series, the mean values were: D_{90} = 4.08 Gy (range: 3.9-4.5 Gy), equivalent to 90.8% of the reference dose of 4.5 Gy; V_{100} = 94.1% (range: 91-95%); V_{150} = 24.7% (range: 20-42%); V_{200} = 10.1% (range: 8-13%). The mean values of homogeneity index (HI) and dose non-uniformity ratio (DNR) were estimated to be 0.71 (range: 0.63-0.75) and 0.39 (range: 0.28-0.42), respectively. The various dosimetric outcomes are shown in Tables 4 and 5.

Discussion

Our retrospective study was aimed to assess the survival rates and toxicity assessment in the patients undergoing reirradiation with HDR-BRT in head and neck malignancies, both as radical treatment and as a boost following EBRT. The literature review has shown that the role of brachytherapy has been used extensively in the past, but non-sorted consensus has not seen brachytherapy as a modality of choice. The literature review with conventional LDR BRT suggests a 2-year LCR of 30% to 80% [15,16,17].

On comparison of the results in literature with external beam irradiation, the 2-year local control rate varies from 20% to 60% [18,19,20,21]. Even with the advent of technologies and the use of IMRT growing, the toxicity

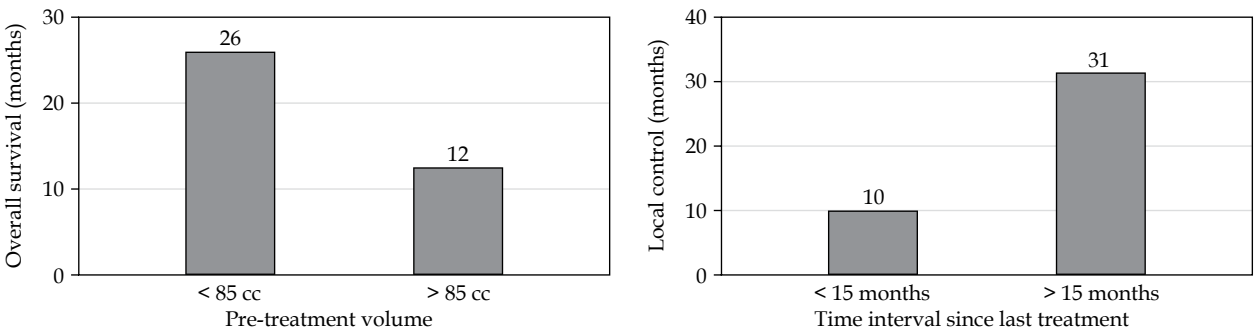

Fig. 3. Prognostic factors on multivariate analysis

Table 4. Dose delivered and treatment parameters

Parameters	Values
Median implant volume	85 cm^3
EBRT total dose	mean: 47.62 Gy median: 46 Gy (9-41 Gy)
BRT dose following EBRT	mean: 22.88 Gy median: 22.5 Gy (21-65 Gy)
Radical BRT dose	mean: 40.72 Gy median: 44.5 Gy (16-53 Gy)
Mean interval between EBRT and BRT	16 days
Post EBRT response	
Complete	81.2%
Partial	18.8%
Follow-up duration	25 months (6-84 months)

EBRT – external beam radiation therapy; BRT – brachytherapy

Table 5. Dosimetric parameters

Dosimetric parameters	Value
D_{90}	4.07 Gy (range: 3.9-4.5 Gy)
V_{100}	73.33% (range: 62-95%)
V_{150}	23.7% (range: 18-41%)
V_{200}	12.52% (range: 11-25%)
Homogeneity index (HI)	0.71 (range: 0.61-0.75)
Dose non-uniformity ratio (DNR)	0.37 (range: 0.29-0.41)

D_{90} – dose received by 90% of the volume; Vx – volume receiving x% of the dose

levels with brachytherapy have found to be better compared to the newer treatment advents due to the advantage provided by brachytherapy of sharp dose fall beyond the target volume, thereby sparing the normal tissues without compromising on the target volume. The 2-year overall survival of 68% and local control rate of 75% reported in our study has been comparable to the one reported in the literature. Better control rates with radical brachytherapy implants as compared to EBRT + BRT shows that in microscopic residual and small volume disease, interstitial brachytherapy can prove to be an effective salvage option for head and neck malignancies and provide better survival outcomes with effective target coverage. In our study, median survival calculated for patients who underwent re-irradiation with HDR-BRT at 1 and 2-year overall survival was found to be 77% and 68%, respectively. The median time to development of a recurrence was found to be 9 months, and was found to be more w frequent in larger tumor implant (CTV > 85 cc) and more common in the EBRT + BRT arm. The local control rate with radical BRT vs. BRT as boost following EBRT was found to be significant. (2-year LCR 62% vs. 85%; $p < 0.02$). The role of brachytherapy as the sole treatment modality can thus be considered in cases with small tumor volume, which eventually would lead to improved local control, disease specific, and overall survival.

Acute and late toxicities form a major limiting factor for opting for radiation therapy as a salvage treatment option in recurrent head and neck malignancies. The toxicities can outweigh the benefits of therapy and result in negative impact on therapeutic index. In the RTOG 99-11 trial, 8% grade 5 (fatal) toxicity and 23% grade 4 acute toxicities were reported [22]. The RTOG 96-10 trial [19] had reported 15% grade 4 and 7% grade 5 toxicities. In our series, cumulative incidence of grade 1 and 2 toxicities at 2-years were 12% and 8%, respectively, and no grade 4 and 5 toxicities were reported. The use of external beam radiation therapy itself can be a difficult modality to be used for salvage option in recurrent head and neck malignancies, as the benefit of therapy can be outweighed by the associated treatment toxicities. Both RTOG studies do not report the delayed toxicities; however, the use of brachytherapy has shown in our series to prevent the severe late toxicities due to the advantage of sharp dose fall off.

The latest report by GEC-ESTRO [23] has reported on the role of HDR-BRT as a salvage option in re-irradiation in the head and neck malignancies. If the patient's ineligible for surgical salvage, brachytherapy is an acceptable option provided that the coverage of the CTV is adequate and there is not advanced bone invasion, fistula, or limited life expectancy. Brachytherapy in previously full course irradiated regions needs to follow the same principles as primary brachytherapy with strict dose and volume constraints [24,25]. Additionally, interstitial brachytherapy can play an important role in the treatment of lymph node recurrences of head and neck cancer. Using image-guided interstitial HDR-BRT for re-irradiation of recurrent lymph node metastases of head and neck cancer, local control probabilities on the order of approximately 60-70% have been published [26].

The dose of 3.5-4 Gy per fraction has been found to be effective enough to provide good dosimetric coverage and overall survival control, and can be modified as per the stage of the disease with target volume covered. The total dose can be modified as per the treatment interval and the implant volume, which form important prognostic factors for better survival outcomes. Similar dose rates have been used by Hepel *et al*. [27] and reported a 2-year LCR and survival of 45% and 37%, respectively. Similar outcomes have also been found in another series with a dose rate of 3.2-4 Gy with favorable survival and toxicity outcomes [28]. In our series, we confirm that the dose of 3.5-4 Gy per fraction to a total dose of 30-40 Gy is effective in providing better survival and late toxicity outcomes. Similar doses have been prescribed in various sites of head and neck malignancies treated with HDR brachytherapy as a boost or as radical intent [29].

Conclusions

Re-irradiation of recurrent head and neck cancer is a therapeutic challenge. This retrospective study summarizes our experience with HDR brachytherapy treatment of recurrent head and neck cancer. HDR-BRT seems a viable alternative to surgery and radical EBRT.

Although this was a retrospective series using a small number of patients, our study showed that HDR interstitial brachytherapy demonstrated a better local control probability with an acceptable toxicity in diverse treatment settings. This technique offers dosimetric, radiation safety, and patient comfort advantages.

Disclosure

Authors report no conflict of interest.

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