RESEARCH ARTICLE

Institutional Experience of Interstitial Brachytherapy for Head and Neck Cancer with a Comparison of High- and Low Dose Rate Practice

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Abstract

Aims: To describe our institutional experience with high dose rate (HDR) interstitial brachytherapy (IBT) compared with previously reported results on the low dose rate (LDR) practice for head and neck cancer. Materials and Methods: Eighty-four patients with oral cavity (n=70) or oropharyngeal cancer (n=14) were treated with 192Ir HDR-IBT. Seventy-eight patients had stage I or II tumour. The patients treated with IBT alone (n=42) received 39-42 Gy/10-14 fractions (median=40 Gy/10 fractions). With respect to the combination therapy group (n=42), prescription dose comprised of 12-18 Gy/3-6 fractions (median=15 Gy/5 fractions) for IBT and 40-50 Gy/20-25 fractions (median=50 Gy/25 fractions) for external radiotherapy. Brachytherapy was given as 2 fractions per day 6 hours apart with 4 Gy per fraction for monotherapy and 3 Gy per fraction for combination therapy. Results: Four patients were not evaluable in the analysis of outcome. The primary site relapse rates were 23.8% (10/42) and 68.4% (26/38) in patients treated with IBT alone and combination therapy, respectively (p<0.001). Salvage surgery was performed in 19 patients. The 5-year local control rate was estimated at 62% and the disease-free survival (DFS) rate at 52% for all patients. Local control with respect to T1 and T2 tumours was 84% and 42%, respectively. Conclusions: Our present series on HDR-IBT and the previous report on LDR-IBT for head and neck cancer demonstrated similar DFS rates at 5 years (52%). The rate of regional failure in node-negative patients was <20% in both of our series. HDR-IBT offers similar results to LDR-IBT for head and neck cancer.

Keywords: Brachytherapy - head and neck cancer - high dose rate - interstitial radiotherapy - uniform dose

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Introduction

The organ-preserving strategy for oral cavity and oropharyngeal cancers is pertinent with respect to the anatomic cosmesis and physiologic acts of deglutition, phonation, and airway protection. Brachytherapy is a beneficial alternative to conventional radiotherapy as it allows sparing of adjacent normal tissues, such as the salivary glands, mandible, and mastication muscles. It provides confined radiation with a rapid dose fall-off and short overall treatment time (Mazeron et al., 2009). Surgery or radiotherapy constitutes the primary treatment modality for early-stage head and neck cancer (HNC). The extent of surgery carries considerable implication as to the resultant functional impairment. Furthermore, the addition of post-operative radiotherapy in patients with positive/close margins or lymph node involvement further increases the functional deficit (van Wilgen et al., 2004). The head and neck brachytherapy practice since 1980s has evolved with remote afterloading technique as low dose rate (LDR), and high dose rate (HDR), which eliminates radiation exposure to the medical personnel. The stepping Iridium source for HDR-IBT with the computerized treatment planning allows for an optimized dose distribution.

Most experience with interstitial brachytherapy (IBT) for early stage HNC has been reported using the LDR technique (Mazeron et al., 2002). There have been recent reports of HDR brachytherapy employed as a therapeutic modality for HNC (Glatzel et al., 2002; Nose et al., 2004; Guinot et al., 2010; Bartochowska et al., 2012). However, there is considerable variation in the published series with respect to the HDR dose and fractionation schedules. We report our institutional experience with uniform dose-fraction schedule of HDR-IBT employed as a treatment modality for early-stage HNC. In addition, this article highlights the outcome compared with the previously reported results of LDR-IBT from the same institute and the published literature on both HDR- and LDR-IBT.

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Materials and Methods

The Institute Rotary Cancer Hospital is the oncology division of the All India Institute of Medical Sciences at New Delhi, India. This cancer centre registers 8,000 to 10,000 new patients annually. Between April 2011 and March 2012, a total of 8,633 cancer patients were registered. Patients with HNC comprised 15.3% of the registrations. The patients are evaluated in a multidisciplinary clinic (MDC) by a team of surgeon, radiation oncologist, and a medical oncologist. Eighty-four patients with HNC (squamous cell carcinoma) were recruited for this prospective study after a decision at the MDC for HDR-IBT between the year 2005 and 2011. All patients signed the institutional informed consent form.

The staging work-up comprised of clinical examination, endoscopy, and chest radiography. The tumour staging was as per the AJCC guidelines (Greene et al., 2002). Baseline ultrasonography examination was performed for evaluation of patients with clinical N0 neck. A pre-treatment dental evaluation was carried out for all patients. The patients with T1 or early T2 lesions (≤3cm) were treated with IBT alone. With respect to the patients with bulky T2 (>3cm), T3 or N+ lesions, the total radical dose was derived from both the IBT and EBRT techniques. The interval between these two modalities was of 2 to 4 weeks.

The interstitial implantation was performed under general anaesthesia with elective tracheostomy for base of tongue tumours. The implant was performed using the implantation rules of Paris system. The size of the tumour was measured for the implant. The points for insertion of needles were marked on the surface of the tumour and the skin of the submandibular or face region depending upon the site of the tumour. The implantation was aimed to cover 1 cm margin around the tumour. Stainless steel hollow needles were inserted through transcutaneous approach followed by plastic catheters in a single or double plane. The spacing between the catheters was maintained equidistant in each plane which ranged from 10 to 15 mm. One end of the catheters was blind with an attached button to anchor the catheters inside oral cavity/ oropharynx. The catheters were secured by buttons in submental/submandibular region or face depending upon the site of the implant.

The patients were simulated on the day after the implant procedure. The simulation was performed either by 2-D orthogonal X-ray (n=20) or 3-D computed tomography (n=64) obtained at 3 mm slice thickness. The implanted plastic catheters were loaded with dummy sources for the dosimetry planning. The HDR remote afterloading technique using 192Iridium radioisotope was employed. The plans were generated for microSelectron-HDR-V2 remote afterloading machine (Nucletron BV, Veenendaal, The Netherlands) using PLATO treatment planning system (Nucletron BV, Veenendaal, The Netherlands). The target volume encompassed the implanted catheters. The dwell positions were defined according to the target geometry so as to cover the target with the prescription dose. The dose prescription was based on ICRU-58 guidelines using basal dose points. The plans were optimized such that the volume receiving 200% of prescription dose was below 15-18% of the target volume.

A customized wax-coated lead shield of 3-5 mm thickness was placed in the oral cavity at the time of IBT dose delivery in order to protect the mandibular bone. Our practice followed a uniform IBT dose of 4 Gy per fraction for monotherapy and 3 Gy per fraction for combination therapy with EBRT. All patients received HDR-IBT as twice-daily fractions with an inter-fraction interval of 6 hours. The patients received antibiotics, analgesics, oral hygiene care, and Ryle's tube feeding during their stay at the hospital. None of the patients developed immediate complications in terms of bleeding or infection at the implant site during insertion or removal of catheters.

With respect to patients treated with combination therapy, EBRT was delivered using the thermoplastic immobilization mould. The target volume for EBRT covered the primary tumour and regional neck nodal regions. The patients were treated with either 60Co γ rays or 6 MV X-rays (linear accelerator). A daily fraction size of 1.8 to 2.0 Gy was delivered 5 days per week. The morbidities related to the treatment were recorded during the course of radiotherapy and subsequently at each follow-up visit. The acute and late effects were documented using the RTOG guidelines (Cox et al., 1995). The patients were followed monthly for the first six months, then three monthly for one year, and six monthly thereafter.

The patient and treatment characteristics are summarized in Table 1. The site of primary tumour was as follows: anterior tongue (n=51), buccal mucosa (n=12), lower lip (n=4), base of tongue (n=11), tonsil (n=3), and floor of mouth (n=3). The majority of patients had stage I or II tumour i.e., 47.6% and 45.2% respectively. Double-plane implant was employed in the majority of patients (n=82). The number of catheters ranged from 4 to 10 (median=6). The median and range for the respective isodose volume for IBT in all patients were as follows: V100=12.7 cc (4.6-38.2 cc); V150=5.2 cc (1.6-21.8 cc),

Table 1. Patient and Treatment Characteristics

		Number (%)
Patients		84
Age	Median 50.5 years	
	Range 24-85 years	
Gender	Male	65 (77.4)
	Female	19 (22.6)
Site	Oral cavity	70 (83.3)
	Oropharynx	14 (16.7)
T classification	T1	41 (48.8)
	T2	42 (50)
	T3	1 (1.2)
N classification	N0	78 (93)
	N1	4 (4.8)
	N2	2 (2.4)
Stage	I	40 (47.6)
	II	38 (45.2)
	III	4 (4.8)
	IVA	2 (2.4)
Treatment modality		
Brachytherapy alone		42 (50)
Brachytherapy with external radiotherapy		42 (50)

and V200=2.3 cc (0.9-14.3 cc).

The patients treated with IBT alone (n=42) received 39-42 Gy in 10-14 fractions (median=40 Gy in 10 fractions). The remaining 42 patients were treated with IBT plus EBRT wherein 21 received IBT followed by EBRT and 18 received EBRT followed by IBT. The remaining three patients did not complete their treatment. With respect to the combination therapy group, IBT dose of 12-18 Gy in 3-6 fractions (median=15 Gy/5 fractions) was delivered with EBRT of 40-50 Gy in 20-25 fractions (median=50 Gy/25 fractions). The IBT course ranged from 5-10 days (median=7 days). The overall treatment time in combination therapy group ranged from 42-74 days (median=57.5 days). The actuarial survival for these patients was summarized by Kaplan-Meier estimates. The patients lost to follow-up were censored at the time of last visit.

Results

The median duration of follow-up was 14 months (range, 1-79 months). The median follow-up for the disease-free patients was 15.5 months. The treatment outcome is illustrated in Table 2. Four patients treated with combination therapy were excluded in the analysis of outcome, as three did not complete the intended therapy and one was lost to follow-up after treatment completion. However, the life table analysis was carried out for all 84 patients as an intention to treat cohort. The observed disease failure rate was analyzed for the 80 patients, and it was 50% (40/80) at the time of reporting. Both local and regional failure was seen within 6 months of treatment completion in the majority of patients (local in 31 out of 36 and regional in 10 out of 11). The primary site relapse rates were 23.8% (10/42) and 68.4% (26/38) in patients treated with IBT alone and IBT plus EBRT combination, respectively ($p<0.001$). With respect to the combination therapy group, local failure was seen in 85% (17/20) and 50% (9/18) of patients treated with IBT followed by EBRT and EBRT followed by IBT, respectively ($p=0.02$). Twelve patients with T1 and 23 with T2 tumour developed local failure. Five patients with T1 and six with T2 tumour developed nodal failure. Nine of the 11 patients with regional failure had presented with N0 neck at baseline. Regional failure was seen in 12% (5/42) and 15.8% (6/38) of patients treated with IBT alone and combination therapy, respectively ($p=0.61$). The patients with oral cavity cancer developed regional neck failure in the following nodal levels: level Ia (n=1), level Ib (n=1), level II (n=8), and level II+III+IV (n=1).

At the time of disease failure detection, salvage therapy was feasible in 32 out of the 40 patients; the remaining eight were unsuitable. Salvage surgery was performed in 19 out of the 32 patients (59%). The remaining 13 patients were non-compliant or defaulted for further treatment with resultant progressive disease. Out of the 19 patients, 6 patients with local failure also underwent elective neck dissection. However, there was no evidence of malignancy in the resected nodes on histopathological examination. Fourteen surgically salvaged patients showed disease control while the remaining five had residual/recurrent

Table 2. Treatment Outcome: Disease Failure After High dose Rate Brachytherapy

Characteristic	Total	Local	Regional	Local+ Regional	Regional+ Distant
All patients	40	29	3	7	1
IBT alone	13	8	2	2	1
IBT with EBRT	27	21	1	5	0
Oral cavity	35	24	3	7	1
Oropharynx	5	5	0	0	0

Values indicate number of patients; Abbreviations: IBT = Interstitial brachytherapy; EBRT = External beam radiation therapy; Note: No. of patients with no evidence of disease at last follow-up = 54 (after salvage therapy of 14/40 failure patients)

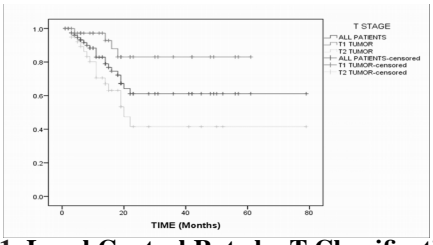

Figure 1. Local Control Rate by T Classification and for all Patients Treated with HDR Brachytherapy

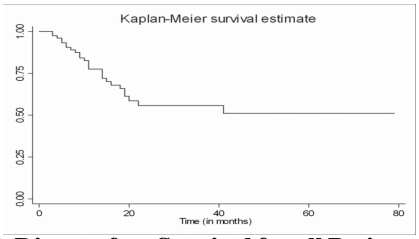

Figure 2. Disease-free Survival for all Patients Treated with HDR Brachytherapy

disease during this observation period. Eleven patients with local, one with regional, and two with loco-regional failure were successfully salvaged with surgery. Adjuvant external radiotherapy, as re-irradiation was delivered in 6 of the 14 patients. One patient received adjuvant chemotherapy after salvage surgery.

At the time of last follow-up, 90% (36/40) patients with T1 and 59% (23/39) patients with T2 primary tumour were disease-free at the local site ($p=0.002$). The 5-year local control (LC) and disease-free survival (DFS) rate for all patients was estimated at 62% and 52% respectively (Figure 1, 2). The 5-year LC rate for patients with T1 and T2 tumour was estimated at 84% and 42%, respectively (Figure 1). With respect to patients treated with IBT alone, mucositis of grade 2 and 3 was seen in 9 and 1 patient respectively (23.8%). As for combination therapy group, grade 2 and 3 mucositis was seen in 15 and 4 patients respectively (45.2%). None of the patients developed osteo-radionecrosis or soft-tissue necrosis during this study period.

Discussion

The existing practice of brachytherapy for HNC patients, either as LDR or HDR, needs to be viewed so as to establish its due place in cancer care. With the advent of the multi-leaf collimator, image-based volumetric radiation dose prescription, intensity-modulated or image-

Table 3. Results of the Studies on HDR Brachytherapy and Comparison of LDR- with HDR Brachytherapy in Head and Cancer

Author, year	No. of patients	Site	Treatment	IBT	EBRT	Results
HDR						
Glatzel et al., 2002	90	HNC recurrent/ residual	IBT alone	4-42 Gy/ 1.5-7.5 Gy per fr		OS 28% (recurrent tumours) OS 84% (residual tumours)
Nose et al., 2004	82	OPX	EBRT+IBT (n=68) IBT alone (n=14)	21 Gy/3.5 fr/2days 48 Gy/8 fr/5 days	46 Gy	5-yr LC 82% 5-yr RC 84% 5-yr CSS 88% 5-yr OS 64%
Guinot et al., 2010	50	Tongue	EBRT+IBT (n=33) IBT alone (n=17)	18 Gy/3 Gy per fr 44 Gy/4 Gy per fr	50 Gy	3-yr DFS 81% 5-yr DFS 74%
Bartochowska et al., 2012	156 PDR (n=106) HDR (n=50)	HNC recurrent	IBT alone (n=156) IBT+CT (n=8 IBT+HT (n=16))	HDR 12-30 Gy/3-10 fr	-	1-yr survival 40% 2-yr survival 17%
LDR versus HDR						
Inoue et al., 2001	51 LDR (n=26) HDR (n=25)	Tongue	IBT	LDR 70 Gy/4-9 days HDR 60 Gy/10 fr/1 week	-	5-yr LC 84% vs 87%
Kakimoto et al., 2003	75 LDR (n=61) HDR (n=14)	Tongue	EBRT+IBT IBT alone	LDR median 68 Gy/1 week HDR median 48 Gy LDR median 72 Gy/1 week HDR 60 Gy/10 fr/5 days	12.5-60 Gy	3-yr LC 67% vs 71%
Yamazaki et al., 2003	399 LDR (n=341) HDR (n=58)	Tongue	IBT	LDR median 70 Gy HDR median 60 Gy	-	5-yr LC 80% vs 84%
Umeda et al., 2005	180 LDR (n=78) HDR (n=26)	Tongue	IBT (n=104) Surgery (n=71)	LDR 61 Gy/5-6 days HDR 59 Gy/9-10 fr	-	Stage I: 5-yr OS 84% vs 72.9% II: 5-yr OS 72.2% vs 51.5%
Ghadjar et al., 2012	103 LDR (n=70) HDR (n=33)	Lip	IBT (n=68) Excision with IBT (n=35)	LDR median 60 Gy HDR median 36 Gy	-	5-yr LRFS 93% vs 93% 5-yr RRFS 87% vs 96% (NS) 5-yr OS 77% (all patients)
Mohanti et al., 2001 and the present report	190 LDR (n=106) HDR (n=84)	OC OPX	EBRT+IBT (n=119) IBT alone (n=71)	LDR median 25 Gy HDR median15 Gy/5 fr LDR median 60 Gy HDR median 40 Gy/10fr	50 Gy 40-50 Gy	5-yr DFS 52% vs 52%

Abbreviations: HDR=High dose rate; LDR=Low dose rate; IBT=Interstitial brachytherapy; EBRT=External beam radiation therapy; HNC=Head and neck cancer; Fr=Fraction; OS=Overall survival; OPX=Oropharynx; LC=Local control; RC=Regional control; CSS=Cause-specific survival; DFS=Disease-free survival; PDR=Pulsed dose rate; CT=chemotherapy; HT=Hyperthermia; LRFS=Local recurrence-free survival; RRFS=Regional recurrence-free survival; NS=Not significant; OC=Oral cavity

guided radiotherapy during the last 15 years or so, it seems appealing to treat early oral or oropharyngeal tumours with EBRT. Furthermore, there is a decline in the radiation oncology community to practice brachytherapy for HNC. Often the modern radiation technology is adapted quickly into practice. An overall analysis of standard versus innovative treatments in radiation oncology showed a preference for standard treatments in 71% of the RTOG trials conducted from 1968 to 2002 (Soares et al., 2005). Despite newer advanced technology in EBRT techniques, which allows a more conformal and optimized radiation to the tumour, brachytherapy should remain an indispensable therapeutic modality in the armamentarium of a radiation oncologist treating HNCs. The Cochrane database review showed no significant difference between HDR- and LDR intracavitary brachytherapy with respect to overall survival (OS), disease-specific survival, LC, and treatment-related complications for women with cervical carcinoma (Wang et al., 2010). Worldwide, majority of the radiotherapy centres have switched to HDR brachytherapy because of its emphasis for gynaecological indications. Besides, the same equipment system can be employed for head and neck, and other suitable sites.

There has been a considerable experience with LDR-IBT for HNC. However, there are limited reports to show comparative evaluation of the different dose rates of IBT for HNC. It has been seen that observational studies (cohort or case-control) show similar summary results as with randomized, controlled trials challenging the current consensus about a hierarchy of study designs in clinical research (Concato et al., 2000). In our institution, 192Ir wire based manual LDR brachytherapy was practiced from 1991 to 2002. Since 2003, the IBT for HNC has been switched over to the HDR remote controlled practice. The present article is a cohort comparison of HDR-IBT in HNC with the previously reported results of LDR-IBT from the same institution (Mohanti et al., 2001). With respect to LDR-IBT, the primary and nodal recurrence was recorded in 38.7% (41/106) and 17% (18/106), respectively. The respective rates in the current study on HDR-IBT are 45% (36/80) and 13.8% (11/80). The implant site failure was more common after combined treatment as compared to LDR-IBT alone i.e., 42.8% versus 27.5% (p=0.15). The current study also reveals a higher local failure rate with combination therapy as compared to HDR-IBT alone (68.4% versus 23.8%). The regional failure in node-negative patients was 19.7% (17/86) in the LDR series while it is 11.5% (9/78) in the current HDR series (NS). The OS and DFS rates with LDR-IBT were 87% and 52%, respectively. A similar DFS rate of 52% has been recorded

in the present study.

The HDR-IBT confers a dual clinical advantage of a short overall treatment time and a reduction in the irradiated volume of normal tissue. The American Brachytherapy Society recommends a dose of 40-50 Gy EBRT followed by 20-35 Gy HDR-IBT for oral cavity tumours (Nag et al., 2001). The current consensus by GEC-ESTRO (Mazeron et al., 2009) recommends LDR-IBT dose of 65-75 Gy for <4 cm tumours of mobile tongue. The EBRT dose of 40-45 Gy with LDR-IBT boost 25-30 Gy has been recommended for >3-4 cm tumour or N1 lesions of tongue. A dose of 45-50 Gy EBRT and HDR-IBT boost of 21-30 Gy in 3 Gy fractions or 16-24 Gy in 4 Gy fractions has been recommended for oropharyngeal tumours of size <5cm.

We have summarized the limited available literature on HDR- and LDR-IBT in HNC for comparison. The results of published series, which consisted of 50 patients or more, and showed the outcome as local control and/or survival are listed in Table 3. The majority of published literature is related to IBT practice for oral and oropharyngeal cancer. The results with HDR-IBT have been shown to be similar to those of LDR-IBT from different institutes (Inoue et al., 2001; Kakimoto et al., 2003; Yamazaki et al., 2003; Umeda et al., 2005; Ghadjar et al., 2012). The results with HDR-IBT demonstrate a 5-year LC of 82% to 84%, 5-year OS of 64% to 77%, and 5-year DFS of 52% to 74% (Table 3).

The current study shows a 5-year LC rate after HDR-IBT of 62%. The LC rate is better for T1 as compared to the T2 tumours (84% versus 42%). A relevant finding from our HDR cohort illustrates that the usage of combination therapy with a lesser dose of IBT (12-18 Gy in 3-6 fractions; median=15 Gy/5 fractions) for T2 tumours of >3 cm size may have resulted in the poorer outcome. A better outcome has been observed when a higher dose of IBT is employed with less or no EBRT (Nag et al., 2001; Guinot et al., 2010). Early detection and treatment of disease failure improves the overall disease control rates. The various HDR-IBT series report incidence of 0-29% and 0-8% for soft-tissue- and osteo-necrosis, respectively (Inoue et al., 2001; Kakimoto et al., 2003; Yamazaki et al., 2003; Nose et al., 2004; Guinot et al., 2010; Ghadjar et al., 2012).

The management of neck with reference to patients treated with IBT remains an area of concern. A wait-and-see policy is often recommended for early oral cancer. A routine policy of elective neck dissection for clinically negative lymph nodes would subject a significant proportion of patients to an unnecessary treatment. The rate of occult nodal metastases in early-stage oral cancer has been reported in the range of 20% to 40% (Borgomeester et al., 2008; Okura et al., 2009; Wensing et al., 2010; Ganly et al., 2012). Avoidance of neck dissection aids in maintaining the deglutition, voice, and movements. Yamazaki et al examined the prognostic factors for lymph node metastasis after IBT in 571 patients with early (T1/T2N0M0) oral tongue cancer (Yamazaki et al., 2004). Multivariate analysis demonstrated ulceration (p=0.006) and tumour thickness of ≥5mm (p=0.04) to be statistically significant predisposing factors for lymph node metastasis. Masuda et al evaluated the immunohistochemical expression of CD44H in 38 cases of primary T1/T2N0 tongue cancer treated with IBT (Masuda et al., 2000). The group of patients developing late nodal metastases revealed a significantly lower CD44H expression (p=0.0035).

A report (Urashima et al., 2006) assessed the functional outcome after IBT in 57 patients with mobile tongue carcinoma over a follow-up period of 9-214 months. None of the patients showed grade 3 atrophy where the tongue could not be made to protrude beyond the incisors. The understandability of speech was preserved in 98% of the patients and 93% could take normal diet.

In conclusion, our present series on HDR-IBT and the previous report on LDR-IBT for HNC demonstrated similar DFS rate at 5 years. The rate of regional failure in node-negative patients was <20% in both of our series. The practice of brachytherapy without external radiotherapy yielded a better disease-related outcome in the two cohorts of our experience. Brachytherapy practice in HNC shows greater than 60% disease control. With radiobiologically equivalent doses, a switch from LDR to HDR offers advantages of personnel safety and better dose optimization.

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