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CLINICAL INVESTIGATION

Intensity Modulated Radiation Therapy Alone Versus Intensity Modulated Radiation Therapy and Brachytherapy for Early-Stage Oropharyngeal Cancers: Results From a Randomized Controlled Trial

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Purpose: The objective of this study was to compare clinical outcomes of intensity modulated radiation therapy (IMRT) alone versus IMRT + brachytherapy (BT) in patients with T1-T2N0M0 oropharyngeal squamous cell cancers (OPSCC).

Methods and Materials: This open-label randomized controlled trial was conducted at Tata Memorial Hospital, Mumbai, India. Patients with stage I and II OPSCC were considered for IMRT to a dose of 50 Gy/25 fractions/5 weeks in phase I followed by randomization (1:1) to further treatment with IMRT (20 Gy/10 fractions/2 weeks) or BT (^{192}Ir high dose rate, 21 Gy/7 fractions/2 fractions per day). The primary endpoint of the trial was the reduction in xerostomia at 6 months evaluated using ^{99m}Tc salivary scintigraphy. Severe salivary toxicity (xerostomia) was defined as post-treatment salivary excretion fraction ratio <45%. Secondary endpoints were local control, disease-free survival, and overall survival.

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Data Sharing Statement: The data from the trial will not be shared publicly because the trial did not have any data sharing plan at the time of institutional ethics committee approval. However, data will be shared upon reasonable request to the corresponding author.

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Results: Between November 2010 and February 2020, 90 patients were randomized to IMRT (n = 46) alone or IMRT + BT (n = 44). Eleven patients (8 residual/recurrent disease, 2 lost to follow-up, 1 second primary) in the IMRT arm and 9 patients (8 residual/recurrence, 1 lost to follow-up) in the BT arm were not evaluable at 6 months for the primary endpoint. At 6 months, xerostomia rates using salivary scintigraphy were 14% (5/35: 95% CI, 5%-30%) in the BT arm while it was seen in 44% (14/32: 95% CI, 26%-62%) in the IMRT arm (P = .008). Physician-rated Radiation Therapy Oncology Group grade ≥2 xerostomia at any time point was observed in 30% of patients (9/30) in the IMRT arm and 6.7% (2/30) in the BT arm (P = .02). At a median follow-up of 42.5 months, the 3-year local control in the IMRT arm was 56.4% (95% CI, 43%-73%) while it was 66.2% (95% CI, 53%-82%) in the BT arm (P = .24).

Conclusions: The addition of BT to IMRT for T1-T2N0M0 OPSCC results in a significant reduction in xerostomia. This strongly supports the addition of BT to IMRT in suitable cases.

Introduction

External beam radiation therapy (EBRT) for the treatment of early-stage oropharyngeal squamous cell cancers (OPSCC) results in xerostomia, which is one of the most debilitating persistent late toxicities, leading to dryness of mouth, oral discomfort, and poor quality of life (QOL).[1,2] Intensity modulated RT (IMRT) has been proven to reduce long-term toxicities, especially xerostomia, compared with conventional/3-dimensional conformal RT.[3-7] However, there is significant residual xerostomia varying from 28% to 50% at 1 year in different prospective randomized studies.[3-7] Xerostomia reduction with IMRT has reached a plateau, and further improvement of therapeutic ratio therefore will require an improved modality of treatment or a different approach to the treatment.

Brachytherapy (BT) is a well-established technique of radiation that delivers high doses to tumors and results in the sparing of critical structures due to rapid fall-off of the dose. BT has been used in various sites of head and neck as well as other parts of the body. The clinical evidence to support the use of BT in head and neck cancers has been limited to retrospective and nonrandomized observational studies.[8,9] Most of these studies have shown good local control (LC) rates and minimal toxicities.[10] However the use of BT has declined in the last few decades due to a lack of robust evidence and evolving newer less resource intense EBRT techniques.

There has been a debate regarding the superiority of IMRT over BT for both LC and reduction in xerostomia.[11,12] IMRT and BT have been used separately in various institutions, and there are some data available combining the 2 modalities that show improvement in patient QOL.[13] BT boost either in the form of low dose rate, pulse dose rate, or high dose rate has shown to improve QOL in various retrospective series.[13,14] Dosimetrically, BT has been shown to improve the target coverage and protect the normal tissue to a larger extent than EBRT.[15] To our knowledge, use of BT has not been tested in a randomized trial for the reduction in xerostomia in any of the head and neck cancers. The aim of the current randomized trial was to compare IMRT alone with IMRT + BT for the reduction of xerostomia in T1-T2N0M0 OPSCC.

Methods and Materials

Study design and participants

This investigator-initiated, open-label, randomized controlled trial comparing IMRT alone with IMRT + BT for the reduction in xerostomia was conducted at Tata Memorial Hospital, Mumbai, India. Patients with early-stage OPSCC (T1-T2N0M0) were invited to participate in the study. The study was approved by an institutional ethics committee (751) of Tata Memorial Hospital, Mumbai, India. The trial is registered at the Clinical Trials Registry of India (CTRI/2010/091/001329).

The main eligibility criteria included T1-T2N0M0 OPSCC, age >18 years, and tumor topology suitable for BT. Exclusion criteria included advanced-stage disease (T3-4, N1-3M0), history of prior irradiation, and nonsquamous histology. All patients signed the written informed consent.

Randomization and masking

Patients were randomly assigned in a 1:1 ratio to IMRT alone or IMRT + BT using computer-generated block randomization. To avoid bias in the contouring, randomization was done after 15 fractions of phase I of IMRT. Randomization was coordinated by the clinical research secretariat. The randomization was not masked. Both clinicians and patients were informed about the trial arm during phase I of IMRT.

Procedures

All patients were evaluated in a joint clinic with surgical and radiation oncologists, where the decision for radical RT alone was taken. After history and clinical examination, patients were evaluated with investigations including biopsy, direct laryngoscopy or evaluation under anesthesia, routine hemogram, and viral markers. Imaging included contrast-enhanced computed tomography (CECT) scan or magnetic resonance imaging of the face and neck and chest X-ray. Sonography of the neck with fine needle aspiration was considered to rule out nodal involvement in suspicious cases.

Disease mapping was done using detailed clinical diagrams depicting the extensions of the tumor and with clinical photographs. Patients were staged as per the American Joint Committee on Cancer staging seventh edition.

Pretreatment salivary scintigraphy was done in all patients after obtaining informed consent. Patients were also served the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and the head and neck (H&N35) module. Additionally, patients were also served the Xerostomia questionnaire and the Dysphagia questionnaire.[16] Dental evaluation and prophylaxis was done in all patients before RT planning.

A baseline dynamic quantitative ^{99m}Tc pertechnetate salivary scintigraphy was done as per the method described by Klutman et al.[17] The procedure for salivary scintigraphy at our institute has been described earlier.[18] In brief, scintigraphy was performed in a supine position under a gamma camera (Infinia Hawkeye, GE Healthcare) with low-energy, high-resolution collimators. No oral stimulus was permitted for 60 minutes before the procedure. After administration of 15 mCi (555 MBq) of ^{99m}Tc pertechnetate, 30-second sequential frames in anterior view were acquired and stored. Salivary stimulation was provided 15 minutes after injection by ingestion of 5 mL of sialagogue (lemon juice). The study was continued for 10 minutes after sialagogue administration. Regions of interest were drawn around bilateral parotids and submandibular glands by nuclear medicine physicians and corresponding time-activity curves were generated. Background correction was performed using the midline neck region. Time-activity curves were fitted to exponential functions. The salivary excretion fraction (SEF) of an individual salivary gland was quantified by calculating the maximal excretory activity per gland as a fraction of maximal uptake.[18]

Patients were planned for EBRT in a supine position with a 4-point fixation thermoplastic mask. A CECT scan was obtained from nasion until 2 cm below the carina with 2.5- to 5-mm slice thickness. Images were transferred to the Eclipse planning system (versions 8.5, 13.5, 16.5; Varian). Gross tumor volume delineation on the CT scan included all the visible and palpable primary disease. A margin of 10 mm was given to generate the clinical target volume for primary (CTV_P) and was edited from the natural barriers, bone, and air. Comprehensive nodal irradiation of bilateral level II to IV was considered and contoured (CTV_N). CTV_P and CTV_N were combined using Boolean operator tools to form CTV_50/25. A margin of 5 mm was generated from CTV_50/25 for the planning target volume (PTV) and was named PTV_ph I_50/25. Ipsilateral nodal irradiation was not considered in any patient. A formal peer review of the contours was not planned in the study protocol. However, at the beginning of the trial, an informal peer review was done in the first few patients. Fixed-field IMRT (7-9 beams) was used until 2015 and volumetric arc technique after 2015 in our patients. Dose-volume optimizer was used for IMRT in Eclipse version 8.6 up to 2015, and progressive resolution optimizer was used for volumetric modulated arc therapy in Eclipse version 13.5 from 2015. The dose constraints used for planning of IMRT are shown in Table E1.

A phase II plan was also made for all patients before starting treatment. Phase II involved irradiation of the primary alone to a dose of 20 Gy/10 fractions/2 weeks in patients who were randomized to the IMRT arm. PTV_ph II_ 20/10 was generated from CTV_P by giving a 5-mm margin. Inverse-planned IMRT was planned for all patients. The sum plan was evaluated for target coverage and sparing of critical structures.

IMRT plan quality assurance was done for each patient individually. The patient-specific quality assurance program involved both point dosimetry using an ionization chamber and fluence verification using a detector array as well as portal dosimetry. The gamma passing criteria >95% with a dose difference of 3% and distance to agreement of 3 mm was considered acceptable.[19] Tata Memorial Hospital follows Technical Report Series number 398 dosimetry protocol recommended by the International Atomic Energy Agency for absolute dosimetry.[20] The institute has periodic dosimetry audits of treatment units by the Imaging and Radiation Oncology Core (Houston, TX) and the Secondary Standard Dosimetry Laboratory (BARC India) as well as accreditation for different international trial participation.

All patients have been treated with image guided RT using either Trilogy, Novalis Tx, or TrueBeam (Varian Medical Systems). Our image guidance protocol included daily imaging with cone beam CT scan for the first 3 fractions with online verification followed by weekly imaging with cone beam CT.

Patients who were randomized to the BT arm were planned for BT 7 to 15 days after completion of phase I of IMRT, depending on the toxicity. BT was done under general anesthesia with endotracheal intubation. Tumor bed, which included pretreatment volume with a 5- to 10-mm margin, was implanted. Steel needles were inserted from the submental or submandibular region depending on the location of the tumor. Steel needles were replaced by plastic catheter tubes. For the base of the tongue, loop technique was used. For the tonsil, 3 to 4 straight catheters were placed; for soft palate, loop technique was considered. The details of the technique have been described elsewhere.[21] BT planning was done using the Oncentra planning system (version 4.1 and 4.3; Nucletron), and the treatment was delivered using an ^{192}Ir high-dose-rate system (Nucletron) to a dose of 21 Gy/7 fractions with 2 fractions per day 6 hours apart. For summation with EBRT dose, equivalent dose in 2-Gy fractions (EQD2) was calculated using linear quadratic model.

Patients were followed up every 3 months for 2 years, every 4 months in the third year, and 6-monthly thereafter.

Outcomes

The primary endpoint of the trial was the reduction in xerostomia evaluated at 6 months. The objective evaluation of

this salivary toxicity was done using salivary scintigraphy. Physician-rated xerostomia was evaluated using Radiation Therapy Oncology Group (RTOG) criteria for acute and late effects.[22] Patient-reported outcomes were measured using the EORTC QLQ-C30, H&N35, and Xerostomia questionnaires. The secondary endpoints of the trial were LC, disease-free survival, and overall survival (OS).

At each follow-up, complete physical examination was done to rule out recurrence. Response assessment with positron emission tomography CECT was done for all patients at 3 months posttreatment. Salivary scintigraphy was done at the 3-, 6-, 12-, and 24-month follow-ups. Patients also filled out the EORTC QLQ-C30, H&N35, Xerostomia, and Dysphagia questionnaires at the 3-, 6-, 12-, and 24-month follow-ups. Human papillomavirus (HPV) testing was done retrospectively using immunohistochemistry p16 as per College of American Pathologists criteria.[23]

Statistical analysis

It was hypothesized that IMRT would result in a reduction in xerostomia by around 50% at 6 months. With the addition of BT, there would be a further 25% reduction in late xerostomia measured at 6 months. The total number of patients needed to evaluate this difference was 131, taking into consideration an alpha error of 0.05 and a beta error of 0.20. Taking into consideration 10% lost to follow-up and another 10% for unsuitability after external radiation or patient refusal, the total sample size calculated was 157 patients over 3 years. However, the trial was closed for further accrual after 90 patients were enrolled due to poor accrual over a period of time and further decrease during the ongoing COVID-19 pandemic. Analysis was done using the intention to treat for the primary and secondary endpoints. Additionally, per-protocol analysis was done for LC.

SEF ratio was defined as the ratio of SEF at a particular time point after treatment compared with the baseline pretreatment SEF × 100%. An SEF ratio of <45% was used as an objective scintigraphic criterion to define severe salivary toxicity, that is, xerostomia. The differences in the 2 groups were compared using the χ^2 test. A P value of <.05 was considered statistically significant.

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS; version 25), R (version 3.6.0), and R studio (version 1.2.1335).

For the patient-reported outcomes, the xerostomia subscale of EORTC H&N35 (ie, Q41: Have you had a dry mouth?) and the Xerostomia questionnaire were used. Of the xerostomia subscale, "quite a bit" and "very much" were considered xerostomia. The 2 treatment groups were compared using the χ^2 test.

For the Xerostomia questionnaire, each item score was added and the sum was transformed linearly to produce the final summary score between 0 and 100, with a higher score suggestive of more xerostomia. The median xerostomia scores of the 2 treatment arms were compared using the Mann-Whitney test.

Time-to-event analysis was done from the RT start date until the event. Survival analysis was done using the Kaplan-Meier method. As the randomization was done after starting treatment to avoid bias in contouring, the RT start date was used for time-to-event analysis. The treatment groups were compared using the log-rank test. Hazard ratios with a 95% confidence interval (CI) were obtained using the Cox proportional hazards model.

Results

Between November 18, 2010, and February 17, 2020, 90 patients with newly diagnosed T1-T2N0M0 oropharyngeal cancers were randomized to IMRT alone (n = 46) or IMRT + BT (n = 44) at Tata Memorial Hospital, Mumbai, India. Figure 1 shows the trial profile as per the Consolidated Standards of Reporting Trials (CONSORT). The baseline patient, tumor and treatment characteristics are given in Table 1. Tobacco usage (chewing/smoking) with or without alcohol was seen in 96% of patients in the IMRT arm and 98% in the BT arm. Comorbidities in the form of hypertension, diabetes, and/or a history of tuberculosis were present in 20% of patients in IMRT and 25% of patients in the BT arm. The predominant T stage was T2 in both groups. The majority of the tumors were HPV negative.

Three patients in the IMRT arm did not complete RT (1 patient did not complete phase I, and 2 did not complete phase II). In the IMRT arm, 8 patients had residual/recurrent disease, 2 were lost to follow-up, and 1 developed a second primary and was not evaluable for primary endpoint at 6 months. Eight patients in the BT arm developed residual/recurrent disease, and 1 patient was lost to further follow-up and thus was not evaluable for the primary endpoint. Hence 32 patients in the IMRT arm and 35 patients in the BT arm were evaluable for intention-to-treat analysis for the primary endpoint of xerostomia reduction (Fig. 1). Seven patients in the BT arm were treated with IMRT boost. This was due to technical feasibility in 5 patients, and 2 patients were unfit for anesthesia. For the secondary endpoint of disease control, all 46 in the IMRT arm and 44 in the BT arm were considered. Overall actual treatment received was IMRT boost in 50 patients and BT boost in 37 patients.

The treatment details are shown in Table 2. The PTV and parotid doses in both arms were comparable in phase I. However, in phase II the average mean parotid dose was 7.02 Gy in the IMRT arm and 1.6 Gy in the BT arm.

Salivary scintigraphy for ipsilateral parotid at 6 months showed a statistically significant reduction in the xerostomia rates with BT (14% [5/35]; 95% CI, 5%-30%) compared with IMRT (44% [14/32]; 95% CI, 26%-62%) (P = .008; Fig. 2). At 12 months, the xerostomia rates in the 2 arms were 31% (9/29; 95% CI, 15%-51%) for the IMRT arm versus 10% (3/29; 95% CI, 2%-27%) for the BT arm (P = .052), and at 24 months it was 20% (5/25; 95% CI, 7%-41%) in the

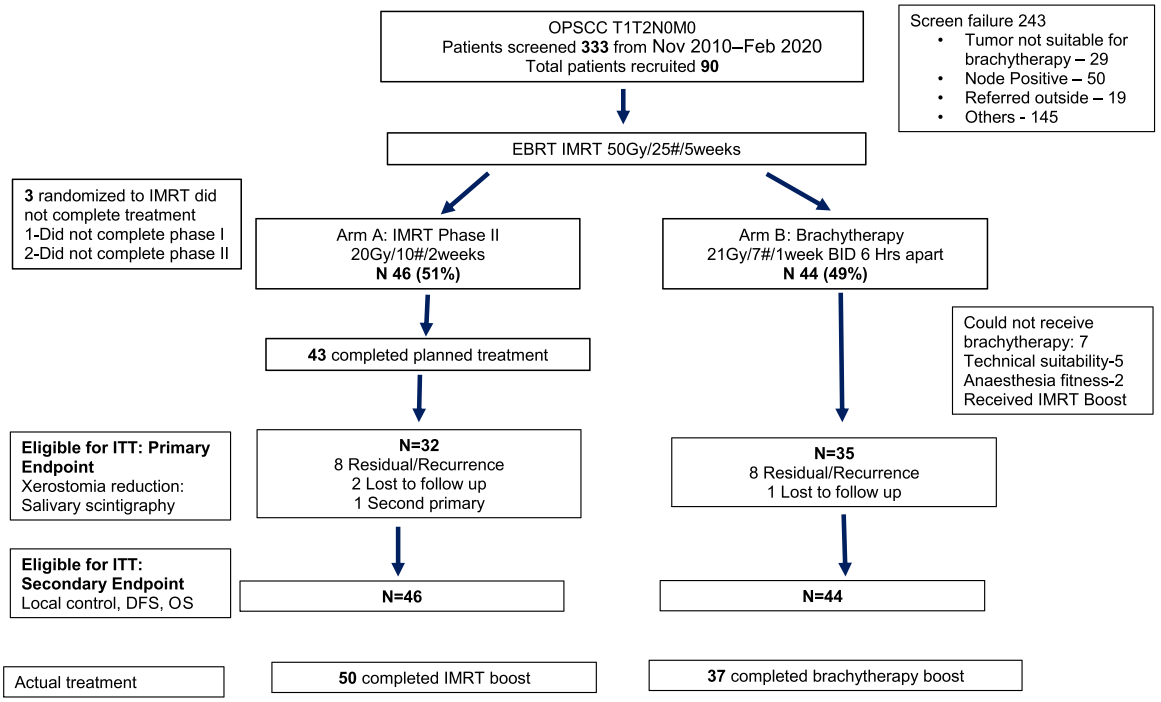

Fig. 1. Trial profile. *Abbreviations:* BID = twice daily; Nov = November; DFS = disease-free survival; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; ITT = intention-to-treat analysis; Feb = February; OS = overall survival; OPSCC = oropharyngeal squamous cell carcinoma.

IMRT arm versus 11.5% (3/26; 95% CI, 2%-30%) in the BT arm ($P = .465$).

The contralateral parotid salivary scintigraphy showed xerostomia rates of 25% (8/32 patients; 95% CI, 11%-43%) in the IMRT arm and 14% (5/35 patients; 95% CI, 5%-30%) ($P = .268$) in the BT arm at 6 months. There was a continued reduction in the xerostomia rates at 12 and 24 months in both arms. The xerostomia rates at 12 months in the IMRT arm were 7% (2/29; 95% CI, 1%-23%) and 14% (4/29; 95% CI, 4%-32%) ($P = -.670$) in the BT arm. At 24 months, the xerostomia rates were 12% (3/25; 95% CI, 3%-31%) in the IMRT arm and 0% (0/26; 95% CI, 0%-13%) in the BT arm ($P = -.110$).

Patient-reported xerostomia using the xerostomia subscale of the EORTC H&N35 module showed xerostomia rates of 36% (10/28; 95% CI, 18%-54%) in the IMRT arm and 31% (11/35; 95% CI, 17%-49%) in the BT arm ($P = .720$) at 6 months. There was a continued reduction in the patient-reported xerostomia rates for both arms at 12 and 24 months.

The median score of the Xerostomia questionnaire at 6 months was 30.63 (17.50, 52.81: 25th and 75th percentile, respectively) in the IMRT arm and 25 (15.63, 36.25: 25th and 75th percentile, respectively) ($P = .173$).

Grade ≥2 RTOG physician-rated xerostomia was observed in 13% (3/24 patients; 95% CI, 3%-32%) in the IMRT arm and 4% (1/27);95% CI, 0%-19%) in the BT arm ($P = .331$) at 6 months. Overall grade ≥2 xerostomia at any time point was observed in 30% of patients (9/30) in the IMRT arm and 6.7% (2/30) in the BT arm ($P = .02$).

RTOG grade ≥2 acute skin toxicity was observed in 23 of 46 patients (50%) in the IMRT arm and in 19 of 44 patients (43.2%) in the BT arm. RTOG grade ≥2 acute mucosal toxicity was seen in 41 of 46 patients (89%) in the IMRT arm and in 33 of 44 patients (75%) in the BT arm.

RTOG grade ≥2 late skin toxicity was seen in 1 of 46 patients (2.1%) in the IMRT arm and in 3 of 44 patients (6.8%) in the BT arm. RTOG grade ≥2 late mucosal toxicity was mainly in the form of mucosal telangiectasia and was seen in 11 of 32 patients (34%) in the IMRT arm and 9 of 35 patients (25%) in the BT arm. There was no case of mucosal necrosis. Two patients in the BT arm and 1 patient in the IMRT arm developed osteoradionecrosis and were managed conservatively.

The median follow-up of the entire cohort was 42.5 months (interquartile range, 20.75-70.25 months). The 3-year actuarial LC in the IMRT arm was 56.4% (95% CI, 43%-73%). There was a 9.8% improvement in LC in the BT arm with a 3-year LC rate of 66.2% (95% CI, 53%-82%), which was not statistically significant ($P = .24$; Fig. 3a). Per protocol analysis of LC was done as 7 patients in the BT arm had received IMRT boost. The 3-year LC rate in patients treated with IMRT boost was 54.3% (95% CI, 42%-70%). There was a 16.7% improvement in the LC rates in patients who received BT boost with a 3-year LC rate of 71% (95% CI, 57%-88%) with a trend toward significance ($P = .076$; Fig. 3b).

The 3-year actuarial locoregional control (LRC) in the IMRT arm was 56.4% (95% CI, 43%-73%) and 60.9% (95% CI, 48%-77%) in the BT arm ($P = .51$). The disease-free

Table 1 Patient and tumor characteristics of the study cohort

Characteristic	IMRT arm (n = 46) Number (%)	Brachytherapy arm (n = 44) Number (%)
Mean age (range), y	56 (34-74)	55 (26-73)
Sex		
Male	41 (89)	42 (95.5)
Female	5 (11)	2 (4.5)
Tobacco/Alcohol Use		
Tobacco (chewing/ smoking)	35 (76)	31 (70.5)
Tobacco (chewing/ smoking)+Alcohol	8 (17.5)	12 (27.5)
Alcohol	1 (2)	0 (0)
No	2 (4.5)	1 (2)
Median duration of habits (IQR), y	20 (2-50)	25 (2-50)
Comorbidity		
Hypertension	3 (7)	4 (9)
Diabetes	1 (2)	2 (4.5)
Diabetes+Hypertension	2 (4.5)	1 (2.5)
Tuberculosis	2 (4.5)	4 (9)
Others	1 (2)	0 (0)
None	37 (80)	33 (75)
Tumor subsite		
Base of tongue	5 (11)	10 (23)
Tonsil	23 (50)	21 (48)
Soft palate	15 (33)	11 (25)
Vallecula	2 (4)	1 (2)
Uvula	1 (2)	1 (2)
Tumor stage (AJCC 7th)		
T1	9 (20)	14 (32)
T2	37 (80)	30 (68)
HPV		
Negative	27 (59)	23 (52)
Positive	5 (11)	3 (7)
Not known	14 (30)	18 (41)

Abbreviations: AJCC = American Joint Committee on Cancer; HPV = human papillomavirus; IMRT = intensity modulated radiation therapy.

survival was 53% (95% CI, 41%-70%) in the IMRT arm at 3 years and 59% (95% CI, 46%-75%) in the BT arm ($P = .93$). The 3-year OS was 68% (95% CI, 55%-83%) in the IMRT arm and 65% (95% CI, 53%-81%) in the BT arm ($P = .39$; Fig. 4).

Discussion

Our trial showed a statistically significant difference in xerostomia rates using salivary scintigraphy at 6 months in favor of BT. There was a significant reduction in overall physician-rated xerostomia at any time point with the use of BT ($P = .02$). To our knowledge, this is the first randomized trial that has shown the reduction of xerostomia with BT over IMRT. While the physician-rated xerostomia also showed reduction at 6 months in the BT arm, it was not statistically significant. The Xerostomia questionnaire showed lower median xerostomia scores in patients treated with BT at 6 months. Similarly, the xerostomia subscale of EORTC H&N35 showed lower subjective xerostomia in patients treated with BT. Although there was a difference between the 2 arms in the subsequent evaluations using salivary scintigraphy, the sample size was not enough to detect the difference as it was calculated for a 6-month time point.

The reduction in xerostomia rates by 30% with the addition of BT to IMRT can have significant implications, especially in the management of HPV-positive cancers. As these patients are long-term survivors, reduction in treatment-related toxicity is an important goal. Reduction in the xerostomia rate has resulted in improvement in QOL in many studies. With xerostomia reduction to only 14%, combining EBRT and BT could be the future strategy in these patients. Although multiple de-escalation studies have been attempted for HPV-positive cancers, a clear advantage of dose de-escalation is yet to be proven. A meta-analysis of all the trials showed that an attempt to de-escalate resulted in inferior outcomes in HPV-positive patients.[24] Due to its ability to produce a rapid fall-off of dose, brachytherapy can provide an opportunity to improve QOL by reducing xerostomia.

We used an objective method of assessment of xerostomia reduction, that is, salivary scintigraphy, along with a comprehensive assessment of xerostomia using both physician-reported xerostomia and patient-reported xerostomia. However, we observed different xerostomia rates with objective and subjective methods in our trial. The lower xerostomia rates in the physician-reported outcomes could be due to the contribution from the other glands which are spared in both IMRT as well as BT. There could also be a bias in physician-rated xerostomia as blinding is not feasible between the 2 treatment techniques. This is true for any RT trial. Differences between physician-reported xerostomia and patient-reported xerostomia are well known and have been documented in various studies.[25-27] Kaae et al observed only a weak correlation between physician findings and patient scores as patients tend to report more xerostomia compared with that of physicians.[26] Salivary scintigraphy, therefore, is the most objective way of evaluating salivary toxicity and xerostomia in the absence of interventions like salivary duct cannulation.

Sparing of the parotid glands has been the primary aim in many IMRT series, including ours.[3,28] This essentially has been due to the contribution of around 60% of the

Table 2 Treatment characteristics of patients enrolled in the trial

Characteristic	IMRT arm (n = 43) Dose (Gy) (Range, SD)	Brachytherapy arm (n = 37) Dose (Gy) (Range, SD)
Median dose to PTV in phase I, IMRT (primary + nodes)	50.4 (46.3-51.5, 0.81)	50.3 (45-51.4, 0.92)
Median dose to PTV in phase II, IMRT arm (primary)	20.18 (19.75-24.28, 0.83)	-
Median EQD2 of D98 of implant volume, brachytherapy arm (primary)	-	23.1 (22.75-28.16)
Mean ipsilateral parotid dose (phase I)	24.3 (9.58-35.26, 4.7)	25.95 (16.70-42.14)
Mean contralateral parotid dose (phase I)	23.6 (12.15-33.5, 4.9)	24.8 (19.28-33.49, 3.2)
Mean EQD2 ipsilateral parotid dose (phase II)	7.02 (2.64-13.98, 2.6)	1.6 (0.52-3.69, 0.87)
Mean EQD2 contralateral parotid dose (phase II)	4.23 (1.80-9.86, 1.7)	0.69 (0.26-1.19)

Abbreviations: D98 = dose received by 98% volume ; EQD2 = equivalent dose in 2-Gy fractions; IMRT = intensity modulated radiation therapy; PTV = planning target volume.

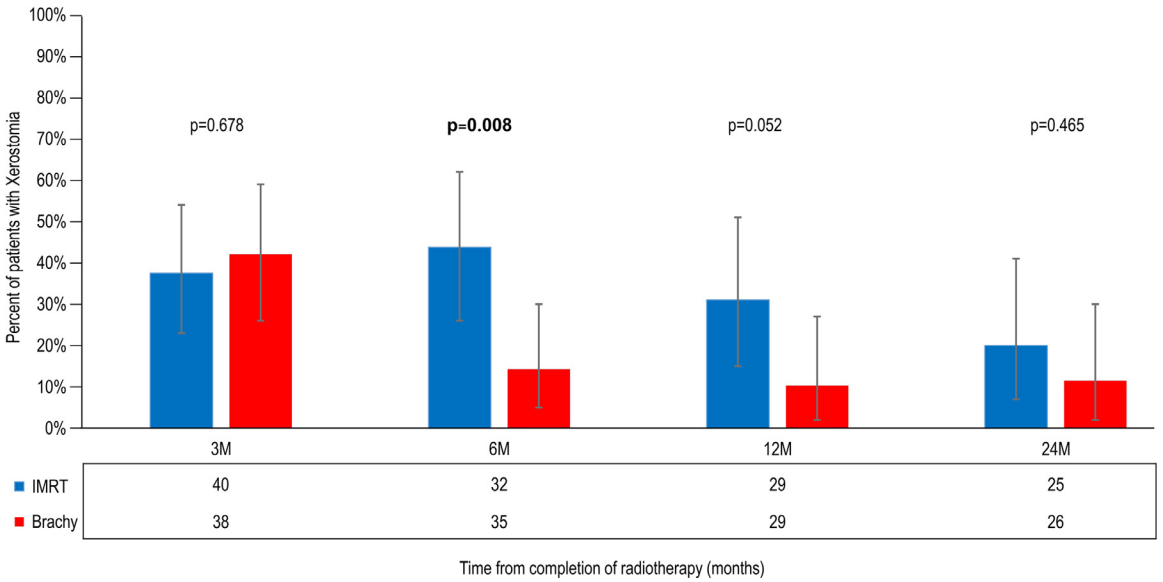

Fig. 2. Salivary scintigraphy of ipsilateral parotid showing the proportion of patients with xerostomia in intensity modulated radiation therapy (IMRT) and brachytherapy (brachy) arms.

stimulated saliva by the parotid glands. Submandibular glands contribute around 20% to 30%, and sublingual glands contribute around 2% to 5% of the stimulated saliva.[29] In the resting state, submandibular glands contribute to around 90% of the saliva. Hence there has been increasing interest in the sparing of submandibular and minor salivary glands. In a study by Eisbruch et al, oral cavity mean dose was an independent predictor of xerostomia.[16] Attempts have been made to spare the submandibular salivary glands using IMRT, and dose-response relationships have been established.[30,31] Contribution of these salivary glands, therefore, cannot be ignored. The dose-volume relationship of submandibular glands in this trial will be the subject of a separate report.

We observed a difference of 9.8% in the LC rates between the 2 arms in favor of BT. This difference, however, was not statistically significant (P = .24). As 7 patients could not be treated with BT due to reasons cited earlier, we also performed per protocol analysis for LC which showed a 16.7% improvement in the LC with the addition of BT with a trend toward significance with a P value of .076. Our trial was not powered to detect a significant difference in the LC. Very few modalities of treatment have shown such improvements in the LC rates. This trial, therefore, provides an opportunity to improve QOL in better prognosis HPV-positive early-stage OPSCC while improving QOL as well as outcomes in poor-prognosis HPV-negative oropharyngeal cancer.

We observed a 3-year LRC of 60.9% (95% CI, 48%-77%) in the BT arm and 56.4% (95% CI, 43%-73%) in the IMRT arm. This improvement of 4.5% was not statistically significant (P = .51). Being a predominantly HPV-negative cohort, lower LRC is expected compared with HPV-positive

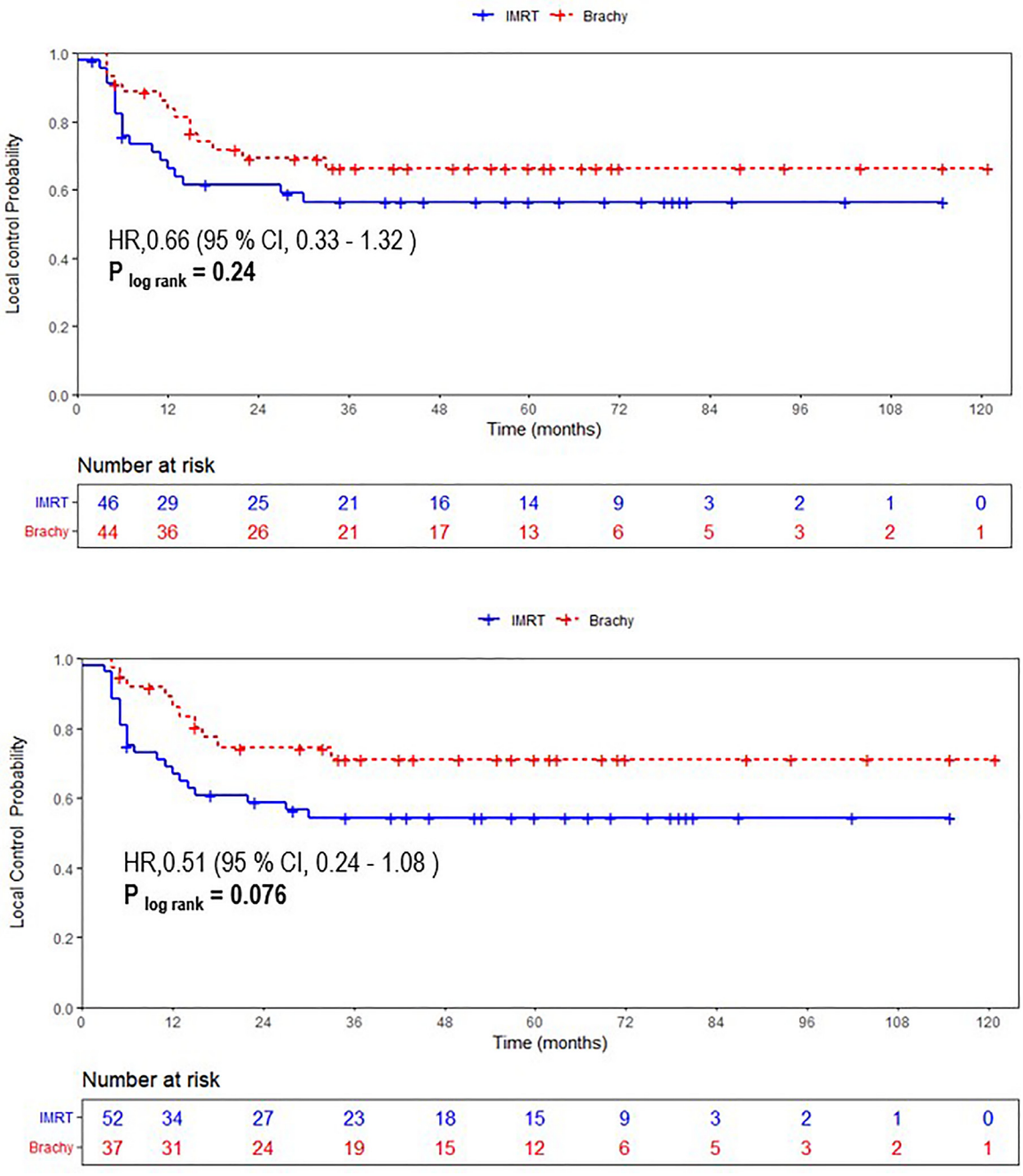

Fig. 3. Kaplan-Meier plot of local control by treatment arm as per (a) intention-to-treat analysis and (b) per-protocol analysis. *Abbreviations:* Brachy = brachytherapy; HR = hazard ratio; IMRT = intensity modulated radiation therapy.

cancers.[32-34] However, our LRC rates are lower compared with the literature. Huang et al reported a 3-year LRC rate of 85% in HPV-negative head and neck cancers treated with IMRT and hypofractionation.[35] We believe prolonged tobacco usage with a median duration of 20 years in more than 90% of patients could have possibly resulted in lower LRC in our series. Prolonged tobacco usage has been shown to have an adverse effect on LRC rates.[32,36] Outcomes from this trial are comparable to our historical cohort as well as recent data.[37,38]

The 3-year OS of 68% and 65% in our series are comparable with 5 year OS of 68% for HPV-negative stage II OPSCC from the ICON-S study.[39] In an analysis from the National Cancer Database, an OS rate of 60% was observed for stage I HPV-negative OPSCCs while it was 56.9% for stage II.[40]

BT is a well-established modality for the treatment of many cancers. However, its inclusion into routine care has been limited in head and neck cancers due to lack of well-conducted randomized trials evaluating efficacy and

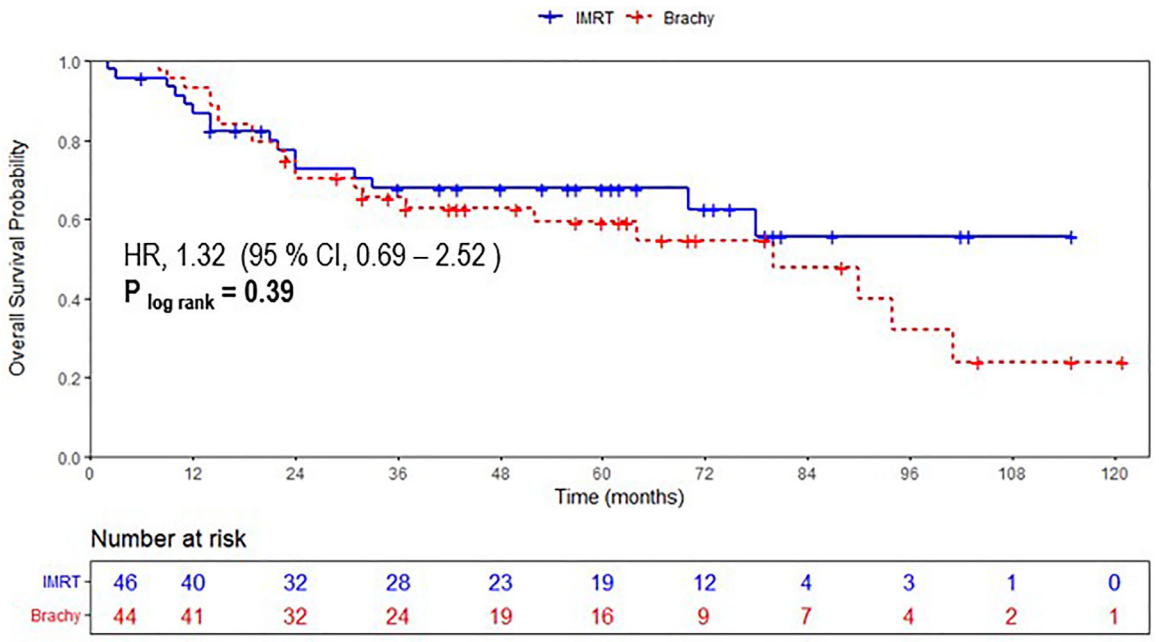

Fig. 4. Kaplan-Meier plot showing overall survival by treatment arm. *Abbreviations:* Brachy = brachytherapy; HR = hazard ratio; IMRT = intensity modulated radiation therapy.

toxicity. There are very few randomized trials comparing BT, mainly limited to breast, esophageal cancers, and soft tissue sarcomas.[41-43] In head and neck cancer, there have been retrospective and prospective data that has shown benefit with BT.[9,13,44] Randomized trials in head neck BT have been limited to nasopharyngeal cancers.[45] There has been no randomized comparison of BT with modern RT for non-nasopharyngeal head and neck cancers. In addition, there is a lack of expertise as well. This has led to reduced utilization of BT. This trial therefore gains importance, and the results obtained are compelling for the use of BT as a standard of care in suitable cases.

One of the drawbacks of this study was the prolonged accrual period. However, there were no major changes in the treatment throughout this time. Another drawback could be an inability to reach the target accrual. We did a post hoc power analysis accounting for the difference in the xerostomia rates obtained in the 2 groups. A sample size of 68 patients was required to detect a 30% absolute difference in the incidence of xerostomia using salivary scintigraphy between IMRT (44%) and BT (14%) assuming an alpha error of 0.05 and a beta error of 0.20 (1-tailed test of significance). This shows the adequacy of the current sample size to detect the obtained difference.

We have used gross tumor volume with a 10-mm margin as CTV as per the prevailing literature. These margins are much larger compared with the current guidelines given by Grégoire et al in 2018.[46] We have used a PTV margin of 5 mm based on our institutional data.[47] A margin of 5 mm with the use of a 4-clamp thermoplastic mask has been shown to be adequate in head and neck cancer.[48] Our image guided RT protocol included daily verification for the first 3 days followed by weekly verification. This may not be an ideal situation because variations tend to occur later in IMRT for head and neck cancer. Further PTV could also be reduced with daily image guidance, and many centers now use 3-mm PTV. Reduction in the CTV and PTV margins could also reduce the parotid doses with EBRT.

One of the important issues is the implementation of trial results in routine clinical practice considering the need for appropriate training, expertise, and the resultant decline in the usage of BT. A survey conducted a few years back showed many residents in training did not have adequate exposure to BT.[49] Another study showed that there was a decline in exposure to interstitial techniques.[50] However there are teaching programs by various BT societies which could be helpful in training for such procedures.

While there is always a quest for finding better and more effective modalities of treatment for improving outcomes, this trial has shown that combining the use of modern EBRT with the existing well-established technique of BT can be complimentary. BT, therefore, appears to be an irreplaceable component of contemporary cancer care in suitably selected patients with the ability to improve disease outcomes and reduce treatment-related sequelae.

Conclusion

The addition of BT to IMRT for the treatment of T1-T2N0M0 oropharyngeal cancers results in a significant reduction in xerostomia. BT should therefore be strongly considered in addition to IMRT for suitably selected T1-T2N0M0 OPSCCs.

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