Received:
24 November 2014

Revised:
8 January 2015

Accepted:
2 February 2015

doi: 10.1259/bjr.20140795

Cite this article as:

Chakraborty S, Patil VM, Babu S, Muttath G, Thiagarajan SK. Locoregional recurrences after post-operative volumetric modulated arc radiotherapy (VMAT) in oral cavity cancers in a resource constrained setting: experience and lessons learned. *Br J Radiol* 2015;88:20140795.

FULL PAPER

Locoregional recurrences after post-operative volumetric modulated arc radiotherapy (VMAT) in oral cavity cancers in a resource constrained setting: experience and lessons learned

¹S CHAKRABORTY, MBBS, MD, ²V M PATIL, DM, MD, ³S BABU, MCh, MS, ¹G MUTTATH, MD, DNB and ³S K THIAGARAJAN, MCh, MS

¹Department of Radiation Oncology, Malabar Cancer Center, Kerala, India

²Department of Medical Oncology, Malabar Cancer Center, Kerala, India

³Department of Surgical Oncology, Malabar Cancer Center, Kerala, India

Address correspondence to: Dr Santam Chakraborty

E-mail: drsantam@gmail.com

Preliminary results of this study have been reported at the Annual Conference of the Federation of Head Neck Oncology held at Chandigarh in September 2014.

Objective: The conformal nature of dose distribution produced by volumetric modulated arc radiotherapy (VMAT) increases the risk of geographic miss. Data regarding patterns of failure after VMAT in oral cavity cancers in resource-constrained settings are scarce. The aim of the present study was to ascertain the patterns of failure in patients receiving adjuvant VMAT intensity-modulated radiotherapy (IMRT) for oral cavity cancer in Malabar Cancer Center, Kerala, India.

Methods: Data of patients with oral cavity cancer receiving adjuvant VMAT IMRT between April 2012 and March 2014 were collected. Recurrent volumes were delineated on the treatment planning images and classified as defined by Dawson et al (Dawson LA, Anzai Y, Marsh L, Martel MK, Paulino A, Ship JA, et al. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy

for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2000; 46: 1117–26).

Results: 75 patients with a median follow-up of 24 months were analysed. 41 (55%) patients had oral tongue cancers and 52 (69%) of the patients had Stage IVA cancers. The 2-year locoregional recurrence-free survival, disease-free survival and overall survival were 88.9%, 82.1% and 80.5%, respectively. With a median time to failure of 6.5 months, five infield and three outfield failures were identified.

Conclusion: A relatively low rate of outfield failure and lack of marginal failure attests to the efficacy of VMAT in such patients. Modifications to our existing target delineation policy have been proposed.

Advances in knowledge: The use of standardized target delineation methods allows safe use of VMAT IMRT even in resource-constrained settings.

Intensity-modulated radiotherapy (IMRT) is considered to be the standard of care for delivering radiotherapy to the head–neck region. The use of IMRT has resulted in the reduction of long-term side effects such as xerostomia, dental caries and laryngopharyngeal dysfunction compared with conventional three-dimensional conformal radiotherapy.^{1–3} However, IMRT is also associated with greater resource use,⁴ as a result its use is restricted to limited numbers of patients in most teaching hospitals in India.⁵ Volumetric modulated arc IMRT (Rapid Arc™; Varian® Medical Systems, Palo Alto, CA) holds promise in this respect as the delivery time is significantly reduced.⁶

One of the problems that may be associated with highly conformal therapy is the risk of marginal failure.^{7,8} While several authors have presented results of adjuvant radiotherapy using IMRT for oral cavity malignancies, no Indian series has been reported till date.^{9–16} Since April 2012, we have been treating patients with head–neck cancers regularly with Rapid Arc IMRT unless the patient had financial difficulties. A high risk of recurrence in the setting of post-operative IMRT has been reported by Turaka et al,¹⁷ who reported that all three marginal failures in their cohort were noticed in patients receiving post-operative radiotherapy. Given the high patient burden and resource

constraints in our setting, it was felt that the use of adjuvant volumetric modulated arc radiotherapy may also result in a similarly increased risk of marginal recurrences in our population. Hence, the present study was designed to audit the disease control-related outcomes as well as to identify the patterns of failure in patients with oral cavity cancers treated with adjuvant radiotherapy using Rapid Arc IMRT. We hypothesized that a 1-year marginal failure rate exceeding 5% may indicate the need for alterations in our target volume delineation practices.

METHODS AND MATERIALS

Patient selection

Patients treated with adjuvant Rapid Arc IMRT for squamous cell carcinomas of the oral cavity after undergoing surgery in our institute were included in this study. Patients completing adjuvant radiotherapy from April 2012 to March 2014 were eligible for inclusion. Exclusion criteria were patients treated with pre-operative radiation or neoadjuvant chemotherapy prior to surgery, non-oral cavity primary site, surgery or chemotherapy

received outside our institute and patients who had received radiotherapy to the head–neck region previously.

Target volume delineation

All patients underwent planning CT with contrast if renal function was normal. Individualized thermoplastic immobilization was prepared for each patient. The departmental guidelines followed for target volume delineation of the tumour bed are shown in Appendix A (Table A1). The neck node levels delineated depended on the primary site and stage. Nodal target volume was delineated following the guidelines proposed by Grégoire *et al.*¹⁸

The high-risk clinical target volume (CTV) included the tumour bed as defined in Table 1 and the nodal levels where nodes were found to be positive. The remaining neck nodes felt to be at risk of recurrence were included in low-risk CTV. Bilateral neck nodal irradiation was given to all patients with tongue or floor of the mouth cancers. In addition, we gave bilateral neck radiation to all patients with buccalalveolar complex cancers who were

Table 1. Demographic profile and surgical details in the patient population

Variable	Parameter	Result
Age (years)	Median (interquartile range)	60 (52.0–65.5)
Gender	Male	47 (62.7%)
	Female	28 (37.3%)
Habits	Smoking	30 (40.0%)
	Chewing tobacco	53 (70.7%)
	Alcohol	31 (41.3%)
Charlson comorbidity index	0	56 (74.7%)
	1	17 (22.7%)
	2	2 (2.7%)
Primary site	Tongue	38 (50.7%)
	Floor of the mouth	3 (4.0%)
	Buccal mucosa	19 (25.3%)
	Alveolus	12 (16.0%)
	Hard palate	1 (1.3%)
	Retromolar trigone	2 (2.7%)
Ipsilateral neck dissection	Supraomohyoid	26 (34.7%)
	Modified radical	44 (58.7%)
	Radical	5 (6.7%)
Contralateral neck dissection	Supraomohyoid	14 (18.7%)
	Modified radical	2 (2.7%)
Mandibulectomy	No	35 (46.7%)
	Yes	40 (53.3%)
Reconstruction	Yes	67 (89.3%)
	No	8 (10.7%)

Sum of values is higher than 75 for habits as 35 patients used multiple habit forming substances.
10 patients had no habits reported.

node positive or had T4 disease. In these cases, the contralateral neck included Level II (from the level where the digastric muscle crosses the internal jugular vein) to Level IV lymph nodal regions. Level IIB nodes were covered in all cases.

Organs at risk (OARs) delineated for all patients included the spinal cord, the brain stem, both parotid glands, pharyngeal constrictors, middle ear cavity, the inner ear, the larynx, the cervical oesophagus, the mandible and normal oral cavity. The spinal cord and brain stem contours were expanded isotropically by 5 mm to generate the respective planning OAR volumes. The details of contouring protocol for the OARs are provided in Appendix A (Table A3).

Dose prescription

Two planning target volumes (PTVs) were defined: PTV high risk (PTV 1) obtained by expanding the high-risk CTV by 5 mm and PTV low risk (PTV 2) obtained by expanding the low-risk CTV by 5 mm. PTV 1 was prescribed a dose ranging between 60 and 66 Gy at 2 Gy per fraction depending on the risk factors. In patients with positive node, positive margins or extracapsular spread higher doses (64–66 Gy) were delivered. PTV 2 was given a dose ranging from 54 to 56 Gy.

Two forms of IMRT were planned: sequential and simultaneous integrated boost depending on physician preference. In sequential IMRT, patients received a dose of 56 Gy in 2 Gy fractions to PTV 1 plus PTV 2 following which PTV 1 alone was boosted to a dose of 60–66 Gy. In simultaneous integrated boost plans, PTV 1 received a dose of 60–64 Gy in 30–32 fractions (2 Gy per fraction) while PTV 2 received a dose of 50–56 Gy in 30–32 fractions (1.8 Gy per fraction).

Rapid Arc planning

Rapid Arc IMRT plans were generated on the Eclipse™ (Varian Medical Systems) treatment planning system v. 10 using 2–3 coplanar monoisocentric arcs. Arc angles were decided according to the target volume geometry with patients requiring bilateral neck radiation being treated with 360° arcs. Organ dose constraints followed the QUANTEC recommendations with spinal cord and brain stem being the Priority 1 organs at risk. Optimization was carried out using the progressive resolution optimization algorithm (PRO v. 10) for a maximum of 177 control points per arc, after which calculation was carried out using the anisotropic analytical algorithm on a 0.25-mm grid.

All patients received treatment for 5 days from Monday to Friday. Concurrent chemoradiation was delivered to patients with extracapsular spread in nodes or positive margins.¹⁹ When planned, concurrent chemoradiation was planned using weekly intravenous cisplatin at a dose of 40 mg m⁻².²⁰

Set-up verification was carried out using kilovoltage cone beam CT (CBCT) scans. The matching procedure included an automatic matching followed by manual adjustment as required. All matches were verified by a senior radiotherapy technician/physician. CBCT scans were acquired on the first 3 days, and any translational errors were corrected. The mean of these errors was used to mark the final isocentre. Subsequent to this, patients

underwent CBCT imaging two–three times per week. If set-up error in any direction exceeded 3 mm, the patients were imaged on consecutive days until the error was not observed. Translational errors >3 mm in any direction were corrected. Based on a previously planned internal audit, we had found that a 5-mm isotropic PTV margin was adequate for accounting for set-up errors observed in our population.

Follow-up

Patients were reviewed weekly during radiation for treatment-related toxicities. Post-treatment follow-up was carried out at monthly intervals in the first year, every 2 months in the second year and every 3 months thereafter. Recurrences, if any, were documented by biopsy. In patients planned for some form of salvage treatment, radiological imaging was obtained.

Definition of failures

Failures were quantified as local, regional and distant. Locoregional failure was defined as any failure above the level of clavicles, including cutaneous failure. All patients with locoregional failure had their plans reanalysed at the time of failure to document the nature of failure (infield, marginal or outfield). The recurrent volume was delineated using anatomical landmarks, clinical examination findings and imaging after rigid registration. We used the definition proposed by Dawson et al²¹ for characterizing the nature of recurrence. Briefly, recurrence was classified as marginal if the 20.0–94.9% of the recurrence volume was within 95% of the prescribed dose. Recurrences with <20% of the volume within 95% prescribed dose were classified as outfield.

Statistical analysis

The study was approved by the institutional review board. Statistical analyses were conducted using R v. 3.1.1 (R: a language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Descriptive analyses included frequencies for categorical variables and median and interquartile range (IQR) for continuous variables. The method of calculating the follow-up period was the one given by Shuster,²² that is, from a Kaplan–Meier curve of the overall survival (OS) reversing the censor and failure variables. The Kaplan–Meier method was used to calculate the actuarial probability of locoregional recurrence-free survival (LRRFS), disease-free survival (DFS) and OS. Duration of survival was calculated from the date of surgery till the date of event or last follow up.

RESULTS

Demographic profile and surgery performed

Subject to the inclusion criteria, 75 patients were selected for the audit out of 125 patients receiving Rapid Arc IMRT for oral cavity cancer (Figure 1). Gingivobuccal complex cancers were present in 33 (44.0%) patients of the patient population and the tongue and floor of the mouth cancers in 41 (54.7%) patients. Table 1 shows the baseline demographic parameters and surgical details for the patients. All patients had European Cooperative Oncology Group performance status 0–1 at baseline. The most common reconstruction techniques included pectoralis major myocutaneous flap, submental artery island flap and facial artery musculomucosal flap in 32 (42.7%), 11 (14.7%) and 10 (13.3%) patients, respectively.

Figure 1. Flowchart showing the reasons for exclusion of patients from the audit. 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; RT, radiotherapy. Rapid Arc™ manufactured by Varian® Medical Systems, Palo Alto, CA.

Pathological findings

Table 2 shows the T and N stage distribution for the patient population. Five patients with Stage I–II cancers had undergone radiation because of positive surgical margins ($n = 1$), multifocal perineural invasion ($n = 3$) and second recurrence in tongue cancer ($n = 1$). The median T size and depth were 2.7 cm (IQR, 2–4 cm) and 1.25 cm (IQR, 0.8–2 cm), respectively. The median number of nodes removed was 25 (IQR, 15.5–34.5). 46 (61.3%) patients had positive nodes, and multiple node positivity was seen in 25 (33.3%) patients. Contralateral nodes were positive in six (8.0%) patients, all of whom had tongue or floor of the mouth cancers.

64 (85.3%) patients had well-differentiated tumours, while 11 (14.7%) patients had moderately differentiated tumours. Extracapsular extension, positive margin and perineural invasion were seen in 8 (10.7%), 1 (1.3%) and 20 (26.7%) patients, respectively. Two (2.7%) patients each had close margins (<5 mm) and dysplasia at the margins.

Radiation treatment details

The median radiation dose was 60 Gy (IQR, 60–64 Gy) to the high-dose PTV and 54 Gy (IQR, 54–56 Gy) to the low-dose PTV. Simultaneous integrated boost IMRT was used in 67 (89.3%) patients, and 64 (85.3%) patients received bilateral neck radiation. Concurrent chemotherapy was delivered in seven (9.3%) patients with the median number of cycles delivered being five. The median delivered chemotherapy dose intensity was 83.3% (IQR, 75.3–91.8%).

The median delay in starting radiation was 43 days (IQR, 35.5–49 days), and the median package time from the date of surgery to the end of radiation was 87 days (IQR, 79–94 days). Package time exceeding 100 days was seen in 12 (16.0%) patients. A gap between surgery and radiation exceeding 50 days was seen in 16 (21.3%) patients, most commonly owing to

logistical problems ($n = 11$) followed by wound complications ($n = 6$). 73 (97.3%) of the 75 patients completed the planned radiation course. 15 (20.0%) patients had a delay of more than 3 days in the delivery of radiotherapy. The most common causes of delays were radiation mucosal and actinic toxicities. Appendix B shows the dose volume parameters achieved for the patient population.

Patterns of failure

The median follow-up for the entire population was 24 months [95% confidence interval (CI), 22–26 months]. Among the patients who were alive, the follow-up period was less than 6, 6–12, 12–18, 18–24 and greater than 24 months in 1, 7, 13, 24 and 17 patients, respectively.

Locoregional recurrences were observed in eight (10.7%) patients of whom one had local, six had nodal and one had cutaneous recurrence in the neck. Distant metastases without locoregional recurrence were seen in a further four patients. The median LRRFS, DFS and OS were not reached (Figures 2–4, respectively). The estimated 2-year LRRFS, DFS and OS were 88.9% (95% CI, 82.0–96.5%), 82.1% (95% CI, 73.6–91.4%) and 80.5% (95% CI, 71.8–91.3%), respectively. All locoregional recurrences were observed within 8 months. Table 3 shows

Table 2. Distribution of pathological T and N stages in the patient population

Pathological stage	N0	N1	N2a–c
T1	2 (2.7%)	6 (8.0%)	7 (9.3%)
T2	3 (4.0%)	6 (8.0%)	11 (14.7%)
T3	6 (8.0%)	0 (0%)	4 (5.3%)
T4a	18 (24.0%)	6 (8.0%)	6 (8.0%)

52 patients had Stage IVA disease.

Figure 2. Kaplan-Meier curve showing locoregional recurrence-free survival for the cohort. Numbers at bottom of the curve represent the numbers at risk at each time point. Dashed lines indicate the 95% confidence intervals of the estimate.

the nature of locoregional recurrences noted in the patient population, baseline details of the patient as well as the nature of recurrence. Infield recurrences in the high-risk CTV and low-risk CTV were seen in three (4%) and two (3%) patients, respectively. None of the patients had a marginal failure and two (3%) of the patients had an outfield failure. Given the small number of recurrences, we failed to find any statistically significant predictors of locoregional recurrence on univariate or multivariate analysis (Appendix C).

Salvage treatment

Salvage treatment in the form of salvage neck dissection was carried out in two patients with outfield failures both of whom had been surviving without disease. Palliative chemotherapy was given to three patients (two with infield and one with outfield recurrence) who progressed and died within 5–7 months

afterwards. Three patients were kept on the best supportive care after detection of recurrence in view of poor general conditions and rapidly progressive disease and died 1–3 months after detection of failure.

DISCUSSION

The present audit confirms the efficacy of adjuvant IMRT in our setting and validates our contouring practice against data from the rest of the world (Table 4). The low rates of local recurrences observed may be related to the low incidence of close or involved margins that were seen in only three (4.0%) patients.²⁵ This is in contrast to reports from western countries where close or positive margins after resection are found in 44–77% of the patients.^{11,23} Also, the incidence of patients with extracapsular tumour extension and perineural infiltration was lower than that reported in western literature despite a higher proportion of T4

Figure 3. Kaplan-Meier curve showing disease-free survival for the cohort. Numbers at bottom of the curve represent the numbers at risk at each time point. Dashed lines indicate the 95% confidence intervals of the estimate.

Figure 4. Kaplan–Meier curve showing overall survival for the cohort. Numbers at bottom of the curve represent the numbers at risk at each time point. Dashed lines indicate the 95% confidence intervals of the estimate.

tumours (Table 4). The reason for this lower incidence may be related to the well-differentiated nature of malignancy encountered in our patient population as well as higher preponderance of the buccoalveolar complex cancers.^{26,27}

Recently, guidelines for target volume delineation have become available in a publication by Liu *et al.*¹⁶ While matching these guidelines in most aspects, some differences in our departmental target delineation policy were noticed. Our tumour bed definition for patients with oral tongue cancers includes the entire residual tongue included in the high-dose CTV. Unlike the guidelines proposed by Liu *et al.*, we do not give a margin around the tumour bed in these patients, which can potentially result in a smaller high-risk CTV. Unlike Damast *et al.*,²⁸ we have not encountered any patient who recurred in the spared portion of the tongue.

Similarly, patients with buccoalveolar complex malignancies had the entire masticator space and infratemporal fossa included in the high-risk CTV. The reason for this was the clinical observation of two failures in the high infratemporal region in two patients treated with telecobalt units previously. This is again more than the definition proposed by Liu *et al.*¹⁶ where a margin around the tumour bed of 20 mm is specified. We have not encountered any recurrences high up in the infratemporal fossa in this series.^{10,23,24}

We have also not encountered flap recurrences unlike the experience reported by Geretschlager *et al.*²⁴ who reported five cases with recurrences within the flap. This is probably related to our policy of encompassing the entire flap within the high-risk or low-risk CTV depending on its location with respect to the nodal volumes. This is also in congruence with the guidelines recently proposed by Liu *et al.*

We also treated the entire ipsilateral neck to elective doses even if the node was negative. This may account for the low regional

recurrence rate seen in the present series (8%) unlike the 16–17% rates experienced in some western series where elective nodal radiation was either omitted or given selectively to patients with N0–1 disease.^{23,29} The majority of our recurrences were in the form of regional nodal recurrences. This replicates the experience of Chan *et al.*²³ where isolated local recurrence was seen in only one patient.

Patient 8 (Table 3) had a nodal recurrence in the Level IV region. In this patient, contralateral nodal radiation was not delivered despite it being T4 tumour, which was against the delineation policy usually followed. The reason for this deviation is unclear but highlights the importance of following our policy regarding contralateral nodal radiation. Our policy of giving contralateral neck nodal radiation is in congruence with that proposed by Liu *et al.*¹⁶

Patient 7 (Table 3) with a T4 tongue lesion recurred in this area, which highlights one of the lacunae in our target delineation policy. We were not irradiating the contralateral Level V in node-negative patients with T4 oral tongue lesions. Our updated target delineation policy given in Appendix A (Table A2) incorporates irradiating this level in addition, which is in concordance with the guidelines proposed by Liu *et al.*¹⁶

It is important to understand the resource constraints at Malabar Cancer Center, Kerala, India. In addition to its rural location, our centre is equipped with a single linear accelerator. On an average, 50 patients are treated each day on this machine with 15- to 20-min time slots for each patient. By contrast, a recent survey conducted by the American Society of Radiologic Technologists showed that the average number of patients treated per machine was 20.1 in the USA.³⁰

Despite the resource constraints, we were able to start radiation for most patients by 7 weeks. This is comparable with western reports where median package times of 5.9–7 weeks have been reported.^{11,13} However, to further reduce this delay, we have

Table 3. The details of the patients with recurrence and the location

Number	Site	Neck dissection (ipsilateral/contralateral)	Stage	Depth of invasion (mm)	Nodal extracapsular extension	Perineural infiltration	Prescribed dose to high-risk/low-risk CTV (Gy)	Bilateral neck radiation	$V_{rec\%}$	V_{rec} D_{mean}	Failure site	Location	Time to failure (months)
1	Tongue	SND	T2N0	0.5	No	Yes	60/54	No	100%	61.18	Remnant tongue/FOM (high-risk CTV)	Infield	5
2	Tongue	SND	T4N2b	1.1	No	No	64/56	Yes	99.8%	66.75	Level III node (high-risk CTV)	Infield	5
3	Tongue	SND	T2N2b	1.2	No	No	60/54	Yes	99.7%	61.99	Level IB node (high-risk CTV)	Infield	5
4	Retromolar trigone	SND	T1N1	0.6	Yes	No	66/56	Yes	98%	58.65	Level II (contralateral) (low-risk CTV)	Infield	7
5	Tongue	MND	T1N1	0.8	No	No	60/54	Yes	97.5%	57.89	Level IV (contralateral) (low-risk CTV)	Infield	6
6	Tongue	MND/SND	T4aN2c	2.0	No	No	60/54	Yes	0%	36.91	Cutaneous recurrence below hyoid in midline (at the level of the high-risk CTV)	Outfield	7
7	Tongue	MND/SND	T4aN0	3.5	No	No	60/54	Yes	0%	38.16	Opposite Level V node (adjacent to low-risk CTV that excluded Level V)	Outfield	8
8	BM	MND	T4aN1	1.4	No	No	60/54	No	0%	11.95	Opposite Level IV node (not in CTV)	Outfield	8

BM, buccal mucosa; CTV, clinical target volume; FOM, floor of mouth; MND, modified radical neck dissection; RT dose, prescribed dose to high-risk/low-risk CTV; SND, supraomohyoid neck dissection; $V_{rec\%}$, percentage recurrent volume inside 95% dose; V_{rec} , D_{mean} , mean dose to recurrent volume in gray.
 None of the patients had a close or positive margin. Infield recurrence is equal to $\geq 95\%$ of the recurrent volume receiving dose $\geq 95\%$ of the prescribed dose.
 When $<20\%$ of the recurrent volume lies inside the 95% isodose line it is classified as an outfield recurrence.

Table 4. The results of series of patients treated with post-operative intensity-modulated radiotherapy for oral cavity cancers reporting patterns of recurrence

Author	Year	Median follow-up	<i>n</i>	T4 (%)	N+ (%)	Positive margin (%)	Extracapsular extension (%)	Perineural infiltration (%)	Concurrent chemoradiation (%)	Infield (%)	Marginal (%)	Outfield (%)	Median time to failure in months	Locoregional control rate
Chao et al ⁹	1997–2000	24	13	NA	NA	NA	NA	NA	0	2	0	3	7.5	90% (2 year)
Yao et al ¹⁰	1999–2004	18	29	NA	NA	NA	NA	NA	0	1	3	1	4.0	78% ^a (2 year)
Gomez et al ¹¹	2000–2006	28	35	31	63	17	23	56	29	4	2	0	6.0	84% (2 year)
Daly et al ¹³	2002–2009	38	37	17	60	10	23	50	60	4	4	3	9.0	53% (3 year)
Moon et al ¹⁴	2003–2008	32	23	30	74	NA	NA	NA	4	7	1	0	11.0	61% (3 year)
Sher et al ¹²	2004–2009	25	30	23	67	0	20	43	77	2	0	0	9.0	91% (2 year)
Chan et al ²³	2005–2010	34	180	NA	68	17	34	61	26	26	7	5	8.0	78% (2 year)
Geretschlager et al ²⁴	2006–2010	28	53	28	76	25	32	5	47	2	8	2	0.6	79% (2 year)
Hsieh et al ¹⁵	2006–2012	NIR	53	28	64	36	26	23	93	9	0	2	7.0	72% (3 year)
Liu et al ¹⁶	2007–2011	27	41	30	49	15	20	20	61	4	1	1	11.5	85% (2 year)
Present series	2012–2014	24	75	40	61	1	11	27	9	5	0	3	6.5	89% (2 year)

LRC, local control rate; NA, not applicable.

The year at which this is reported is mentioned in parenthesis under LRC.

Publications with a mix of other cancers were reviewed individually to obtain information regarding the patients with post-operative oral cancer.

^aFor oral cavity patients (unknown if it includes definitively treated patients also).

started giving appointments for starting radiation on the date of surgery itself so that radiation treatment can start within 6 weeks of completion of surgery.

The present study is limited by its retrospective nature and the limited follow-up. However, as is seen in Table 4, the majority of locoregional failures in oral cavity cancers after receiving adjuvant radiotherapy recur within 1 year. The experience is also replicated in the present study. In addition to minimizing heterogeneity, we have excluded patients who had undergone other forms of treatment or underwent surgery outside our institute. In most cases involving nodal recurrence, we were not satisfied with the accuracy of rigid registration available in our treatment planning system. The inaccuracy was more apparent in the lower neck region and was owing to the position of the neck in the diagnostic imaging obtained. Furthermore,

owing to a combined effect of flap shrinkage, weight loss and post-radiation fibrosis in all cases, the surface contours moved medially inside after aligning the bony anatomy. As shown by Shakam et al,³¹ the use of deformable image registration may allow better assessment of the dosimetry to the recurrent tumour volume in this setting.

CONCLUSIONS

The present study affirms that post-operative adjuvant IMRT using Rapid Arc when delivered using standardized contouring and planning techniques has a low risk of marginal failures even in high volume centres with resource constraints. Some modifications to the existing target volume delineation guidelines have been proposed based on the results obtained. These results need to be validated over a longer follow-up period.

REFERENCES

- King A. IMRT for head-and-neck cancer improves quality of life and reduces xerostomia. *Nat Rev Clin Oncol* 2006; **3**: 7.
- Duarte VM, Liu YF, Rafizadeh S, Tajima T, Nabili V, Wang MB. Comparison of dental health of patients with head and neck cancer receiving IMRT vs conventional radiation. *Otolaryngol Head Neck Surg* 2014; **150**: 81–6. doi: [10.1177/0194599813509586](https://doi.org/10.1177/0194599813509586)
- Anderson NJ, Rolfo M, Khoo V, Lim Joon D, Handley M, Wada M. IMRT for oropharyngeal carcinoma: improving acute dysphagia and post treatment weight management through superior midline sparing during definitive chemo-radiation. *Int J Radiat Oncol Biol Phys* 2011; **81**: S496.
- Vorwerk H, Zink K, Schiller R, Budach V, Böhmer D, Kampfer S, et al. Protection of quality and innovation in radiation oncology: the prospective multicenter trial the German Society of Radiation Oncology (DEGRO-QUIRO study). Evaluation of time, attendance of medical staff, and resources during radiotherapy with IMRT. *Strahlenther Onkol* 2014; **190**: 433–43. doi: [10.1007/s00066-014-0634-0](https://doi.org/10.1007/s00066-014-0634-0)
- Kaur J, Mohanti BK, Muzumder S. Clinical audit in radiation oncology: results from one academic centre in Delhi, India. *Asian Pac J Cancer Prev* 2013; **14**: 2829–34.
- Oliver M, Ansbacher W, Beckham WA. Comparing planning time, delivery time and plan quality for IMRT, RapidArc and Tomotherapy. *J Appl Clin Med Phys* 2009; **10**: 3068.
- Sanguineti G, Gunn GB, Endres EJ, Chaljub G, Cheruvu P, Parker B. Patterns of locoregional failure after exclusive IMRT for oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2008; **72**: 737–46. doi: [10.1016/j.ijrobp.2008.01.027](https://doi.org/10.1016/j.ijrobp.2008.01.027)
- Studer G, Luetolf UM, Glanzmann C. Locoregional failure analysis in head-and-neck cancer patients treated with IMRT. *Strahlenther Onkol* 2007; **183**: 417–23; discussion 424–5.
- Chao KS, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2003; **55**: 312–21.
- Yao M, Dornfeld KJ, Buatti JM, Skwarchuk M, Tan H, Nguyen T, et al. Intensity-modulated radiation treatment for head-and-neck squamous cell carcinoma—the University of Iowa experience. *Int J Radiat Oncol Biol Phys* 2005; **63**: 410–21.
- Gomez DR, Zhung JE, Gomez J, Chan K, Wu AJ, Wolden SL, et al. Intensity-modulated radiotherapy in postoperative treatment of oral cavity cancers. *Int J Radiat Oncol Biol Phys* 2009; **73**: 1096–103. doi: [10.1016/j.ijrobp.2008.05.024](https://doi.org/10.1016/j.ijrobp.2008.05.024)
- Sher DJ, Thotakura V, Balboni TA, Norris CM Jr, Haddad RI, Posner MR, et al. Treatment of oral cavity squamous cell carcinoma with adjuvant or definitive intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2011; **81**: e215–22. doi: [10.1016/j.ijrobp.2011.02.023](https://doi.org/10.1016/j.ijrobp.2011.02.023)
- Daly ME, Le QT, Kozak MM, Maxim PG, Murphy JD, Hsu A, et al. Intensity-modulated radiotherapy for oral cavity squamous cell carcinoma: patterns of failure and predictors of local control. *Int J Radiat Oncol Biol Phys* 2011; **80**: 1412–22. doi: [10.1016/j.ijrobp.2010.04.031](https://doi.org/10.1016/j.ijrobp.2010.04.031)
- Moon SH, Jung YS, Ryu JS, Choi SW, Park JY, Yun T, et al. Outcomes of postoperative simultaneous modulated accelerated radiotherapy for head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2011; **81**: 140–9. doi: [10.1016/j.ijrobp.2010.04.068](https://doi.org/10.1016/j.ijrobp.2010.04.068)
- Hsieh CH, Kuo YS, Liao LJ, Hu KY, Lin SC, Wu LJ, et al. Image-guided intensity modulated radiotherapy with helical tomotherapy for postoperative treatment of high-risk oral cavity cancer. *BMC Cancer* 2011; **11**: 37. doi: [10.1186/1471-2407-11-37](https://doi.org/10.1186/1471-2407-11-37)
- Liu SH, Chao KS, Leu YS, Lee JC, Liu CJ, Huang YC, et al. Guideline and preliminary clinical practice results for dose specification and target delineation for postoperative radiotherapy for oral cavity cancer. *Head Neck* Mar 2014. Epub ahead of print. doi: [10.1002/hed.23692](https://doi.org/10.1002/hed.23692)
- Turaka A, Li T, Sharma NK, Li L, Nicolaou N, Mehra R, et al. Increased recurrences using intensity-modulated radiation therapy in the postoperative setting. *Am J Clin Oncol* 2010; **33**: 599–603. doi: [10.1097/COC.0b013e3181c4c3cc](https://doi.org/10.1097/COC.0b013e3181c4c3cc)
- Grégoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. *Radiother Oncol* 2006; **79**: 15–20.
- Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931)

- and RTOG (#9501). *Head Neck* 2005; **27**: 843–50.
20. Gupta T, Agarwal JP, Ghosh-Laskar S, Parikh PM, D'Cruz AK, Dinshaw KA. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single-institution experience. *Head Neck Oncol* 2009; **1**: 17. doi: [10.1186/1758-3284-1-17](https://doi.org/10.1186/1758-3284-1-17)
 21. Dawson LA, Anzai Y, Marsh L, Martel MK, Paulino A, Ship JA, et al. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2000; **46**: 1117–26.
 22. Shuster JJ. Median follow-up in clinical trials. *J Clin Oncol* 1991; **9**: 191–2.
 23. Chan AK, Huang SH, Le LW, Yu E, Dawson LA, Kim JJ, et al. Response to letter to the editor with reference to article “Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: patterns of failure”. *Oral Oncol* 2013; **49**: e19. doi: [10.1016/j.oraloncology.2013.02.005](https://doi.org/10.1016/j.oraloncology.2013.02.005)
 24. Geretschlager A, Bojaxhiu B, Crowe S, Arnold A, Manser P, Hallermann W, et al. Outcome and patterns of failure after post-operative intensity modulated radiotherapy for locally advanced or high-risk oral cavity squamous cell carcinoma. *Radiat Oncol* 2012; **7**: 175. doi: [10.1186/1748-717X-7-175](https://doi.org/10.1186/1748-717X-7-175)
 25. Barry CP, Ahmed F, Rogers SN, Lowe D, Bekiroglu F, Brown JS, et al. Influence of surgical margins on local recurrence in T1/T2 oral squamous cell carcinoma. *Head Neck* May 2014. Epub ahead of print. doi: [10.1002/hed.23729](https://doi.org/10.1002/hed.23729)
 26. Shaw RJ, Lowe D, Woolgar JA, Brown JS, Vaughan ED, Evans C, et al. Extracapsular spread in oral squamous cell carcinoma. *Head Neck* 2010; **32**: 714–22. doi: [10.1002/hed.21244](https://doi.org/10.1002/hed.21244)
 27. Shibuya Y, Ohtsuki Y, Hirai C, Hasegawa T, Akashi M, Shigeta T, et al. Oral squamous cell carcinoma with microscopic extracapsular spread in the cervical lymph nodes. *Int J Oral Maxillofac Surg* 2014; **43**: 387–92. doi: [10.1016/j.ijom.2013.09.015](https://doi.org/10.1016/j.ijom.2013.09.015)
 28. Damast S, Wolden S, Lee N. Marginal recurrences after selective targeting with intensity-modulated radiotherapy for oral tongue cancer. *Head Neck* 2012; **34**: 900–6. doi: [10.1002/hed.21677](https://doi.org/10.1002/hed.21677)
 29. Studer G, Brown M, Bredell M, Graetz KW, Huber G, Linsenmeier C, et al. Follow up after IMRT in oral cavity cancer: update. *Radiat Oncol* 2012; **7**: 84. doi: [10.1186/1748-717X-7-84](https://doi.org/10.1186/1748-717X-7-84)
 30. American Society of Radiologic Technologists. *Radiation Therapy Staffing and Workplace Survey 2014*. Albuquerque, NM: American Society of Radiologic Technologists; 2014.
 31. Shakam A, Scrimger R, Liu D, Mohamed M, Parliament M, Field GC, et al. Dose–volume analysis of locoregional recurrences in head and neck IMRT, as determined by deformable registration: a prospective multi-institutional trial. *Radiother Oncol* 2011; **99**: 101–7. doi: [10.1016/j.radonc.2011.05.008](https://doi.org/10.1016/j.radonc.2011.05.008)

APPENDIX A

Table A1. Original departmental guidelines for target volume delineation

Site	High-risk CTV	Low-risk CTV
Buccal mucosa and alveolus	Flap covering entire buccal mucosa excluding oral tongue. Masticator space and infratemporal fossa included along with pterygopalatine fossa Nodal levels where positive	Levels IB–V (ipsilateral) Levels II–IV (contralateral), if N+ or T4 disease Any portion of the flap/sternocleidomastoid muscle adjacent to the nodal levels to be covered in addition if the neck is dissected
Oral tongue and floor of the mouth	Entire tongue and floor of the mouth inclusive of the mylohyoid muscles and Level IB. Hard palate spared by using a tongue depressor Nodal levels where positive	Levels IB–V (ipsilateral) Levels II–IV (contralateral) Any portion of the flap/sternocleidomastoid muscle adjacent to the nodal levels to be covered in addition if the neck is dissected
Hard palate	Entire hard palate, maxillary sinus, soft palate and lower half nasal cavity. In case of tumour extension into the nasal cavity, the entire nasal cavity including ethmoid sinuses. A tongue depressor would be placed to spare the oral tongue Nodal levels where positive	Levels IB–V (bilateral) Levels II–IV (contralateral), if N+ or T4 disease Any portion of the flap/sternocleidomastoid muscle adjacent to the nodal levels to be covered in addition if the neck is dissected
Retromolar trigone	Masticator space plus infratemporal fossa up to pterygopalatine fossa flap plus ipsilateral buccal mucosa ipsilateral tonsil, tonsillar pillars and lateral pharyngeal walls Nodal levels where positive	Levels IB–V (ipsilateral) Levels II–IV (contralateral), if N+ or T4 disease Any portion of the flap/sternocleidomastoid muscle adjacent to the nodal levels to be covered in addition if the neck is dissected

CTV, clinical target volume.

Table A2. New guidelines followed for target volume delineation

Site	High-risk CTV	Low-risk CTV
Tongue and floor of the mouth	The entire residual tongue and floor of the mouth inclusive of the base of the tongue and the mylohyoid muscle plus any flap Any nodal levels where positive nodes	Ipsilateral Level IA–V nodes, if N0; Level VB in addition, if N+ Contralateral Levels IB–V, if N0, otherwise Level VB also to be included Level VI, if Level IV involved
Alveolus/buccal mucosa	Entire ipsilateral buccal mucosa, masticator space and infratemporal fossa, including the pterygopalatine fossa plus the flap for reconstruction Any nodal levels where positive nodes	Ipsilateral Levels IA–IV nodes, if N0 Ipsilateral Levels IA–V, if N+ Contralateral Levels IB–IV, if N+ or T4 Contralateral Levels IB–V, if contralateral node positive
Hard palate	Entire residual palate plus soft palate. Maxilla and the nasal cavity up to the level of the orbital floor if uninvolved (otherwise entire nasal cavity and ethmoid air cells) Any flap Any nodal levels where positive nodes	Ipsilateral Levels IA–IV nodes, if N0 Ipsilateral Levels IA–V, if N+ Contralateral Levels IB–IV, if N+ or T4 Contralateral Levels IB–V, if contralateral node positive
Retromolar trigone	Entire ipsilateral buccal mucosa, masticator space, infratemporal fossa, ipsilateral tonsil, base of tongue, soft palate and flap Any nodal levels where positive nodes	Ipsilateral Levels IA–IV nodes if N0 Ipsilateral Levels IA–V, if N+ Contralateral Levels IB–IV, if N+ or T4 Contralateral Levels IB–V, if contralateral node positive

CTV, clinical target volume.

Note that midline involvement of the tongue/FOM/palate means there will be no contralateral nodes.

Any portion of the flap/sternocleidomastoid muscle adjacent to the nodal levels to be covered in addition if the neck is dissected.

Table A3. The delineation protocol for organs at risk (OARs) and associated dose constraints

OAR	Delineation protocol	Constraints
Spinal cord	The entire spinal canal from the level of where the brain stem ends to the level of the lower border of the T4 vertebrae PORV: isotropic expansion of 5 mm	$D_{\max} \leq 45 \text{ Gy}$ $D_{\max} \text{ PORV} \leq 50 \text{ Gy}$
Brain stem	From the level of the posterior clinoid process to the level where the odontoid process of C2 is visible PORV: isotropic expansion of 5 mm	$D_{\max} \leq 50 \text{ Gy}$ $D_{\max} \text{ PORV} \leq 54 \text{ Gy}$
Middle ear	Air-containing cavity anterolateral to the inner ear and limited laterally by the ear drum	$D_{\text{mean}} \leq 30 \text{ Gy}$
Inner ear	The cochlea and vestibular canals	$D_{\text{mean}} \leq 30 \text{ Gy}$
Pharyngeal constrictor	5-mm thick structure including the lateral and posterior pharyngeal wall extending from the level of the pterygoid hamulus to the level of lower border of cricoid cartilage	$D_{\text{mean}} \leq 50 \text{ Gy}$
Parotid	The entire parotid gland	$D_{\text{mean}} \leq 24 \text{ Gy}$ (I) or both parotid $V_{30} \leq 50\%$ volume (II)
Larynx	The larynx with its cartilages extending from the level of the hyoid to the lower border of the cricoids cartilage	$D_{\text{mean}} \leq 40 \text{ Gy}$
Uninvolved oral cavity	The oral cavity including buccal mucosa as a single structure subtracted from the PTV	As low as possible
Mandible	The entire bony mandible including coronoid process and condyle	$D_{2\text{cc}} \leq 70 \text{ Gy}$
Cervical oesophagus	The oesophagus below the level of the lower border of cricoid cartilage to the level of the upper border of manubrium sterni	Dose of 33% volume $\leq 45 \text{ Gy}$

 $D_{2\text{cc}}$, minimum dose to 2 cm³ volume; $D_{\max}$, maximum point dose; D_{mean} , mean dose to the organ; PORV, planning OAR volume; V_{30} , volume receiving 30 Gy.

APPENDIX B

Table A4. The dose volume parameters obtained for the target volume

Parameter	High-dose PTV	Low-dose PTV
Volume (cm ³)	305.2 (200.9–417.1)	264.8 (179.2–375.8)
D_{98} (%)	98.4 (96.7–98.9)	98.5 (95.7–98.9)
D_2 (%)	107.0 (105.3–108.0)	107.4 (106.7–108.6)
D_{50} (Gy)	62.5 (61.9–65.2)	56.2 (55.8–57.0)
ICRU conformity index	0.95 (0.94–0.96)	0.95 (0.89–0.96)
Homogeneity index	0.19 (0.17–0.21)	0.09 (0.08–0.12)

D_2 , minimum dose to 2% volume (percentage of the prescribed dose for the respective PTV); D_{50} , median dose; D_{98} , minimum dose to 98% of the volume (percentage of the prescribed dose for the respective PTV); ICRU, International Commission on Radiation Units and Measurements; PTV, planning target volume.

Note that low-risk PTVs are lower than high-risk PTVs as they are subtracted from the high-risk PTV for reporting purposes. Median and 95% confidence intervals of median are displayed.

APPENDIX C

Table A5. Cox regression analysis of factors affecting locoregional control, disease-free survival and overall survival

Parameter	Locoregional recurrence	Disease-free survival	Overall survival
Age (years)	0.002 (0.036)	0.016 (0.028)	0.002 (0.026)
Gender (male)	0.016 (0.810)	0.089 (0.625)	−0.239 (0.622)
Charlson comorbidity index (>0)	0.201 (0.771)	0.148 (0.653)	−0.389 (0.705)
Primary site (buccoalveolar complex)	−1.008 (0.881)	−0.348 (0.646)	−0.017 (0.625)
Stage (IVA)	−0.533 (0.822)	−0.134 (0.629)	−0.528 (0.620)
Tumour size (cm)	−0.174 (0.283)	0.126 (0.211)	−0.228 (0.250)
Tumour depth (>4 mm)	18.461 (10,512.400)	18.080 (8550.618)	18.156 (8676.791)
Perineural infiltration (present)	−1.364 (1.090)	−0.372 (0.681)	0.450 (0.583)
Nodal extracapsular extension (present)	−0.178 (1.149)	0.457 (0.830)	1.148 (0.706)
Total package time (days)	0.017 (0.021)	0.007 (0.020)	0.001 (0.021)
Observations	75	75	75
R^2	0.077	0.051	0.088
Max. possible R^2	0.594	0.764	0.783
Log likelihood	−30.830	−52.149	−53.819
Wald test (df = 10)	4.430	2.010	4.700
LR test (df = 10)	6.012	3.947	6.938
Score (logrank) test (df = 10)	5.341	3.174	6.489

df, degrees of freedom; LR, likelihood ratio; max., maximum.

Figures in parenthesis represent the standard error.

None of the factors was statistically significant.