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Does elimination of planned postoperative radiation to the primary bed in p16-positive, transorally-resected oropharyngeal carcinoma associate with poorer outcomes?

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ABSTRACT

Objective: The purpose of our study is to compare oncologic and functional outcomes of p16-positive oropharyngeal squamous cell carcinoma (OPSCC) patients, in the presence and absence of planned radiation to the primary bed following transoral surgery (TOS), stratified by T-classification.
Methods: Retrospective cohort study of 261, T1-T4, consecutively TOS-treated OPSCC patients.
Results: At a median follow-up of 61 months, local recurrence (LR) occurred in 6 (2.3%) patients (3 each in T1-T2 and T3-T4 groups), of which 5 had tumors in the tongue base and one in the tonsil. Of patients not receiving planned primary bed radiation, LR occurred in 3% of T1-T2s versus 17% of T3-T4s. In patients with T1-T2 tumors, Absolute Risk Reduction of LR with primary bed radiation was 3.26% (95% CI: −0.37%, 7%); Number Needed to Treat to prevent one LR was 31 (95% CI: 14.5, 271). Absolute Risk Increase for gastrostomy-tube with primary bed radiation was 34.4% (95% CI: 24%, 45%); Number Needed to Harm was 3 (95% CI: 2.2, 4.2), i.e., for every three patients with T1-T2 tumors receiving primary bed radiation, one had a gastrostomy-tube.
Conclusions: Elimination of primary bed radiation in margin-negative resected, T1-T2 p16-positive OPSCC was not associated with significant compromise of local control, and correlated with superior swallowing preservation, assessed using gastrostomy rate as a surrogate. Lack of primary bed radiation in T3-T4 tumors associated with significantly increased LR rates.

Introduction

Transoral surgery (TOS) for head and neck primaries allows carefully-controlled intraoperative margin analysis, resulting in high margin-negative resection and low local recurrence rates [1–4]. Reported outcomes from observational studies in the literature on oropharynx squamous cell carcinoma (OPSCC) indicate that avoidance of radiation to the primary site may result in good local control although no data specific to human papillomavirus (HPV) or p16-positivity is presented [1,5]. For instance, a 5-year Kaplan-Meier local control of 94% was observed in a series of 69 patients with tongue base tumors (T1-T3) treated with transoral laser microsurgery (TLM) alone, but without HPV/p16 stratification [5].

Amongst OPSCC, p16-positive subtypes have a distinct biology and often present with small primary tumors and advanced regional disease [2,6]. These p16-positive tumors also demonstrate a better overall response to treatment compared to chemical carcinogen-related OPSCC and have a low local recurrence rate, particularly for early stage tumors [2,7]. No comparative data are currently available to judge whether it is safe to avoid radiation to the primary bed in TOS-treated p16-positive OPSCC. Preliminary observational studies do not report reduced oncologic control with de-intensified radiation fields, but these studies are not restricted to p16-positive OPSCC patients or to the elimination of radiation to the primary beds [8–11]. At the study institution, a patient group arises from TOS-treated p16-positive OPSCC patients who did not receive planned primary bed radiation due to

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circumstances such as early primaries with a widely negative margin, patient refusal of any adjuvant radiation, or participation in institutional radiation de-escalation initiatives. This group of patients who did not receive planned primary bed adjuvant radiation enabled a comparative analysis with patients who did receive planned primary bed adjuvant radiation. The specific aim of our study is to assess and compare local control and functional outcomes in transorally-resected p16-positive OPSCC patients in the presence or absence of postoperative primary bed radiation, stratified by T-classification.

Materials and methods

A prospectively-assembled, Institutional Review Board-approved, transoral surgery (TOS) database was used to identify consecutively-treated oropharynx cancer patients from 1996 to 2013. Informed consent was obtained for entry into the TOS database. The eligibility criteria were untreated biopsy-proven OPSCC, p16-positivity on immunohistochemistry, absence of distant metastasis at presentation, transoral resection ± adjuvant therapy, and minimum follow-up of 12 months (Fig. 1). Demographic, pathologic T- and N-classification, treatment, oncologic and functional outcomes data was collected from the TOS-database, verified and updated for the current study. Reporting of our observational cohort study was done in accordance to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist [12].

Radiation technique

Adjuvant radiation by intensity-modulated radiation therapy (IMRT) was delivered at a median time of 6 weeks after surgery. Gross tumor volumes (GTVs) were contoured based on pre-operative physical examination, imaging, operative and pathology reports. Computed tomography (CT) simulation scans were fused

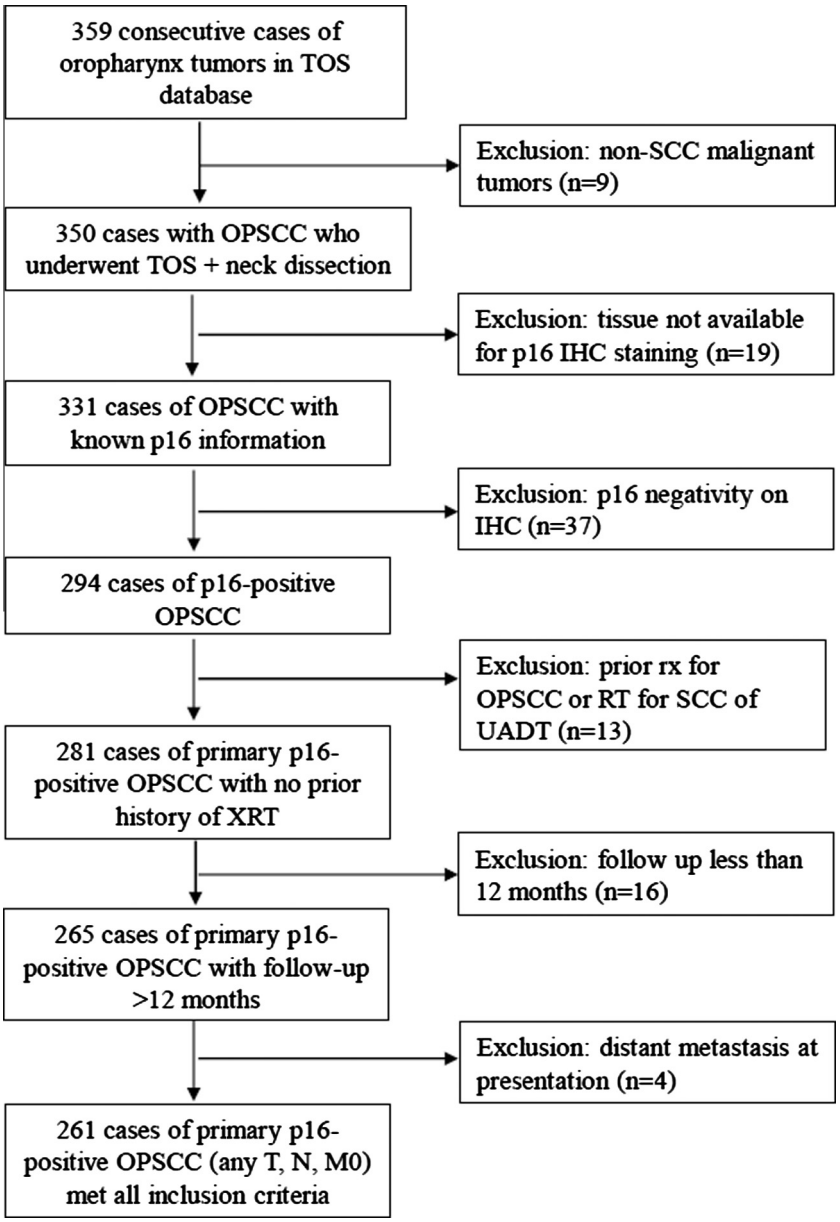

Fig. 1. Flow diagram depicting patient selection TOS-transoral surgery, SCC-squamous cell carcinoma, OPSCC-oropharynx squamous cell carcinoma, IHC-immunohistochemistry, XRT-radiation, UADT-upper aerodigestive tract.

with pre-operative scans. The high-risk clinical target volume (CTV1) was defined as the primary tumor bed (when treated) (pGTV + 1.5–2.0 cm) and positive neck nodes (nGTV + 0.5–1.0 cm) or positive neck nodes alone when the primary tumor bed was not treated. The low-risk or elective clinical target volume (CTV2) was defined as the uninvolved elective neck. These volumes were expanded by 0.5 cm to obtain a planning target volume (PTV). The total dose to the tumor bed was 66 or 60 Gy in 33 or 30 fractions of 2 Gy each over 6–7 weeks. Dose painting was utilized in the elective neck to 54 or 52 Gy in 1.73 or 1.63 Gy per day.

Functional outcomes assessment

Functional outcomes for the study cohort were assessed by the gastrostomy and tracheostomy rates. Prophylactic gastrostomy insertion is an uncommon practice at our institution. It is performed at the discretion of the treating radiation or medical oncologist for patients with comorbidities or when the overall well-being is anticipated to be compromised during adjuvant therapy, even with minimal body weight loss. There is also a group of patients who undergo gastrostomy to supplement nutritional intake in the postoperative period but the gastrostomy-tube is left in place when the swallowing improves, in case it is needed during adjuvant therapy. For reporting of gastrostomy results in patients receiving radiation, this group was considered as part of the group with prophylactic gastrostomy. Reactive gastrostomy tube placement during or after adjuvant therapy is based on observation of weight loss (~10%), significant mucositis or treatment-related gagging or severe nausea causing reduced oral intake. No long-term nasogastric tubes were used in the study cohort.

Statistical analysis

Local recurrence-free survival (LRFS) and local recurrence (LR) were primary oncologic outcomes. Gastrostomy and tracheostomy rates were secondary functional outcomes. Temporary gastrostomy tube and tracheostomy rate referred to their presence during the perioperative and adjuvant therapy period. Sample size could not be calculated since no previous study has investigated elimination of primary bed radiation. All outcomes and variables were compared for patients who received primary bed radiation as a planned radiation target versus those without planned primary bed radiation. These comparisons were stratified by early (T1-T2) and advanced (T3-T4) tumors. Heterogeneity between groups was investigated using Chi-square or Fischer's Exact Test for categorical data and independent *t* test for continuous data. All statistical tests employed were two-sided and statistical significance was indicated at a p value of less than 0.05. LRFS probability with 95% confidence intervals (CI) was estimated by Kaplan-Meier method and compared using the log-rank test. Metrics of Absolute Risk Increase (ARI), Absolute Risk Reduction (ARR), Number Needed to Treat (NNT) and Number Needed to Harm (NNH) were also computed with 95% CIs. Analyses were performed using SPSS software (IBM SPSS Statistics, Rel 23.0.0, Chicago: IBM Corporation).

Results

A total of 261 p16-positive OPSCC patients met the study criteria (Fig. 1). The median follow-up duration for alive and disease-free patients was 61 months (minimum–maximum: 12–199 months). Table 1 describes the demographic, tumor and treatment-related characteristics of the study cohort as stratified by T-classification and delivery or non-delivery of planned primary bed radiation. Overall, the tumor was located in the tongue base in 136 (51%) and tonsil in 125 (49%) patients, and the pT-classification was early (T1-T2) in 202 (77%) and advanced (T3-T4) in 59 (23%) patients.

The primary bed received planned radiation in 157 patients (60%) receiving adjuvant therapy. Primary bed did not receive planned radiation in 104 patients (40%), of which 59 did not receive any adjuvant therapy and 45 patients (44 T1-T2, 1 T3) received only ipsilateral neck radiation. Of these 104 patients, 81 (78%) did not receive adjuvant or planned primary bed radiation under institutional deescalation initiatives after 2009, while the remaining 23 (22%) did not receive radiation due to patient refusal, wide surgical margins and the absence of pathologic features such as perineural or lymphovascular invasion. The local recurrence, gastrostomy and tracheostomy rates stratified by the presence and absence of primary bed radiation and the T-classification are presented in Table 2.

Disease recurrence

Disease recurrence occurred in a total of 30 (11.5%) patients, the site of recurrence being local in 6 (2.3%) patients, regional in 6 (2.3%), distant alone in 15 (5.7%), and regional plus distant in 3 (1%) patients. The T-classification distribution of local recurrence was: 1 in 112 T1s (0.9%), 2 in 90 (2.2%) T2s, 2 in 34 T3s (6%), and 1 in 25 T4s (4%).

Adjuvant therapy and local recurrence

Overall, 59 (23%) patients (48 T1-T2;11 T3-T4) did not receive any adjuvant radiation or chemoradiation, with LR in 5 (8%). There was no LR in the group of 45 patients who received adjuvant radiation to the ipsilateral neck but not to the primary bed. Of the remaining 202 (77%) patients with adjuvant therapy, LR occurred in 1 (0.5%). The ipsilateral neck was treated in all patients with neck dissection and/or radiation. Of the patients receiving adjuvant therapy, 82 (31%) received chemotherapy in addition to radiation.

Margin and local recurrence

The negative-margin resection rate was 96% (n = 193/202) after the primary procedure and 100% after re-resection in T1-T2 patients. The negative-margin resection rate was 88% (n = 52/59) after the primary procedure and 93% (n = 55/59) after re-resection in T3-T4; four patients refused re-resection, three of whom underwent adjuvant therapy. One refused further management and developed LR. Overall, in patients reported to have positive margins on first resection, no LR occurred in the T1-T2 group (6 of 9 received primary bed radiation), whereas one LR occurred in the T3-T4 group (5 of 7 received primary bed radiation).

Local recurrence and functional outcomes by planned primary radiation and T-classification

T1-T2 primaries

Of 202 T1-T2 patients, 92 (46%) did not receive planned primary bed radiation (48 did not receive any adjuvant while 44 received only ipsilateral neck radiation). LR occurred in 3% (n = 3/92) of the patients who did not receive primary bed radiation versus 0% in patients receiving radiation. The ARR of LR with planned primary bed radiation was 3.26% (95% CI: −0.37, 7%). The NNT for preventing one LR was 31 (95% CI: 14.5, −271). Five-year LRFS was 98% (95% CIs: 95.7%, 100%) overall for the T1-T2 patients, and 94% (95% CIs: 85%, 100%) in the group without primary radiation versus 100% in the group with primary radiation, the difference being non-significant (Fig. 2).

The temporary gastrostomy rate was 6.5% (n = 6/92) in patients without planned primary radiation versus 41% (n = 45/110) in

Table 1
Demographic, tumor and treatment characteristics.

Variable	Category	pT1-T2, n = 202 (77%)		pT3-T4, n = 59 (23%)		Total
		Planned primary XRT No n = 92 (46%) n (%)	Planned primary XRT Yes n = 110 (54%) n (%)	Planned primary XRT No n = 12 (20%) n (%)	Planned primary XRT Yes n = 47 (80%) n (%)	n (%)
Age	Median (min-max)	56.5 (36–84)	55 (27.5–77)	64 (49–81.3)	58 (67–75)	56.6 (27.5–84)
Sex						
	Male	74 (80)	94 (85)	11 (92)	43 (92)	222 (85)
	Female	18 (20)	16 (15)	1 (8)	4 (8)	39 (15)
Site						
	Tonsil	46 (50)	54 (49)	4 (36)	21 (44)	125 (49)
	Tongue base	46 (50)	56 (50)	8 (67)	26 (55)	136 (51)
Smoking						
	Never	51 (55)	52 (47)	8 (67)	18 (38)	129 (49)
	Ever	41 (45)	58 (53)	4 (33)	29 (62)	132 (51)
Comorbidity						
	ACE27 0-1	85 (90)	94 (85)	12 (100)	44 (94)	235 (90)
	ACE27 2-3	7 (10)	16 (15)	0	3 (6)	26 (10)
N-classification						
	N0-N2b	85 (92)	94 (85)	11 (92)	29 (62)	219 (84)
	N2c-N3	7 (8)	16 (15)	1 (8)	18 (38)	42 (16)
Margin						
	Negative	89 (97)	104 (95)	10 (83)	42 (89)	245 (94)
	Positive	3 (3)	6 (5)	2 (17)	5 (11)	16 (6)
*ECE**						
	Absent	31 (42)	16 (15)	2 (29)	2 (5)	51(22)
	Present	43 (58)	90 (85)	5 (71)	42 (95)	180 (78)
PNI						
	Negative	90 (98)	102 (93)	10 (83)	32 (68)	234 (90)
	Positive	2 (2)	8 (7)	2 (17)	15 (32)	27 (10)
LVI						
	Negative	76 (83)	84 (76)	7 (58)	20 (43)	187 (72)
	Positive	16 (17)	26 (24)	5 (42)	27 (57)	74 (28)
Adjuvant radiation						
	None	48 (52)	0	11 (92)	0	59 (23)
	Yes	44 (48)	110 (100)	1 (8)	47 (100)	202 (77)

XRT-Radiation; ACE-Adult Comorbidity Evaluation; PNI-Perineural invasion; LVI-Lymphovascular invasion; ECE*-Extracapsular extension only variable with significantly different distribution between patients with and without primary radiation in both pT1-T2 and pT3-T4 groups (p value, $\varkappa^2$ test = 0.001).

Table 2
Local recurrence, gastrostomy (G-tube) and tracheostomy rates.

Outcome	Category	pT1-T2, n = 202 (77%)		pT3-T4, n = 59 (23%)		Total
		Planned primary XRT No n = 92 (46%) n (%)	Planned primary XRT Yes n = 110 (54%) n (%)	Planned primary XRT No n = 12 (20%) n (%)	Planned primary XRT Yes n = 47 (80%) n (%)	n (%)
Follow-up	Median (min-max)	38 (12–138.5)	42.5 (30–123)	93 (21.6–199)	72 (24.4–129)	61 (12–199)
Local recurrence			p = 0.093		p = 0.102	
	None	89 (97)	110 (100)	10 (83)	46 (98)	255 (98)
	Yes	3 (3)	0	2 (17)	1 (2)	6 (2)
Temporary G-tube			$p \leqslant 0.001$		p = 0.053	
	None	86 (94)	65 (59)	8 (67)	16 (34)	175 (67)
	Yes	6 (6)	45 (41)	4 (33)	31 (66)	86 (33)
G-tube at 1-yr			p = 0.04		p = 0.30	
	None	90 (98)	99 (90)	10 (83)	30 (64)	229 (88)
	Yes	2 (2)	11 (10)	2 (17)	17 (36)	32 (12)
G-tube at 2-yr			p = 0.07		p = 1.00	
	None	90 (98)	101 (92)	10 (83)	36 (77)	237 (91)
	Yes	2 (2)[a]	9 (8)	2 (7)	11 (23)	24 (9)
Temporary tracheostomy[b]			p = 1.00		p = 0.51	
	None	85 (92)	102 (93)	9 (75)	29 (62)	225 (86)
	Yes	7 (8)	8 (7)	3 (25)	18 (38)	36 (14)

XRT-radiation.
[a] Of the two patients, one had local recurrence after salvage transoral microsurgery and the second patient had distant metastasis.
[b] All were successfully decannulated except one patient with laryngeal chondroradionecrosis.

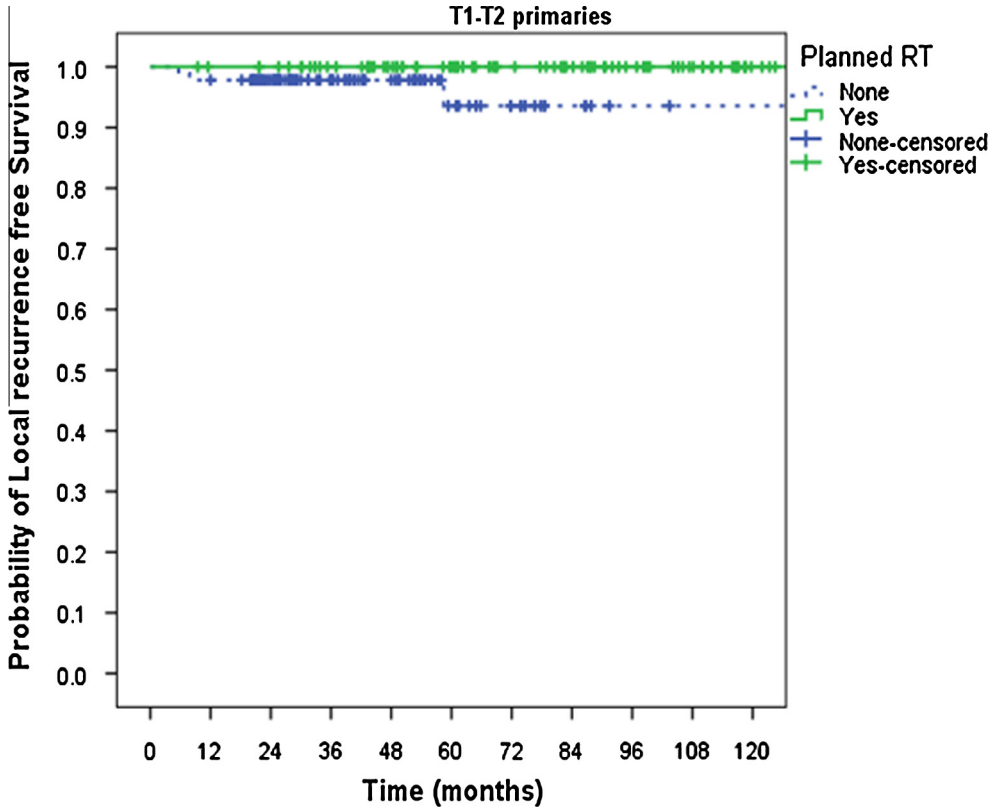

Fig. 2. Kaplan-Meier local recurrence-free survival in T1-T2 patients with and without primary bed radiation (log rank test not computable due to 100% survival in one group).

patients receiving planned primary radiation ($p < 0.001$). Of the 6 patients with gastrostomy tube in the group without planned primary bed radiation, the indications were reactive during or after adjuvant therapy to the neck (n = 3), postoperative nutrition supplementation (n = 2), and recurrent disease (n = 1). Of the 45 patients with gastrostomy tube in the group with primary bed radiation, the indications were reactive (n = 34), prophylactic (n = 8), late swallowing toxicity (n = 2), and could not be determined (n = 1). The ARI for gastrostomy with primary bed radiation was 34.4% (95% CI: 24%, 45%); NNH was 3 (95% CI: 2.2, 4.2), i.e., for every three patients with T1-T2 tumors receiving primary bed radiation, one had a gastrostomy. At two years, the ARI for gastrostomy was 6% (95% CI: 0.1%, 12%); NNH is 17 (95% CI: 8.4, 1217).

The tracheostomy rate of 8% (n = 7/92) in patients without planned primary radiation did not differ significantly from 7% (n = 8/110) in those without radiation. The indications for tracheostomy were recurrence or second primary of the aerodigestive tract (n = 5), post-adjuvant complications of airway edema (n = 3), planned procedure to secure airway at onset or completion of surgery (n = 3), anesthesia complications (n = 2), and postoperative bleeding (n = 2). All patients without recurrent or second primary disease were decannulated except one patient who developed laryngeal chondroradionecrosis.

T3-T4 primaries

Of 59 patients, 12(20%) did not receive planned primary radiation (11 did not receive any adjuvant radiation while one received radiation only to ipsilateral neck). LR occurred in 17% (n = 2/12) of the patients who did not receive planned primary bed radiation versus 2% (n = 1/47) in patients receiving planned primary bed radiation. The ARR of LR with planned primary bed radiation was 14.5% (95% CI: −6.95%, 36%). The NNT for preventing one LR was 7 (95% CI: −14.4, 2.8). Five-year LRFS was 95% (95% CI: 89%, 100%) in the overall T3-T4 group, and 82% (95% CI: 60%, 100%) in the group without planned primary radiation versus 98% (95% CI: 93.5%, 100%) in the group with primary radiation, the difference being significant (Fig. 3).

The temporary gastrostomy rate was 33% (n = 4/12) in patients without planned primary radiation versus 66% (n = 31/47) in patients receiving planned primary radiation (p = 0.053). Of the 4 patients with gastrostomy tube in the group without planned primary bed radiation, the indications were postoperative nutrition supplementation (n = 3) and recurrent disease (n = 1). Of the 31 patients with gastrostomy tube in the group with primary bed radiation, the indications were prophylactic (n = 20), reactive (n = 10), and could not be determined (n = 1). The ARI for gastrostomy with primary bed radiation was 32% (95% CI: 2.7%, 62.5%); NNH was 4 (95% CI:1.6, 37), i.e., for every four patients with T3-T4 tumors receiving primary bed RT, one had a gastrostomy. At two years, the ARI for gastrostomy was 6.74% (95% CI: −17.6%, 31%); NNH was 15 (95% CI: −5.7, 3.2).

The tracheostomy rates were 25% (n = 3/12) in the group without planned primary radiation and 38% (n = 18/47) in the group with planned primary radiation. The indications for tracheostomy were planned procedure to secure airway at onset or completion of surgery (n = 15), post-adjuvant airway edema (n = 1), anesthesia complications (n = 1), postoperative bleeding (n = 1), second primary of the aerodigestive tract (n = 1), preoperative emergent procedure (n = 1) and postoperative ventilation due to altered mental status (n = 1). All patients without second primary disease were successfully decannulated.

Outcomes of patients with local recurrence (n = 6)

Two patients are disease-free after salvage TLM; one had re-recurrence after salvage TLM and is alive with disease; one is

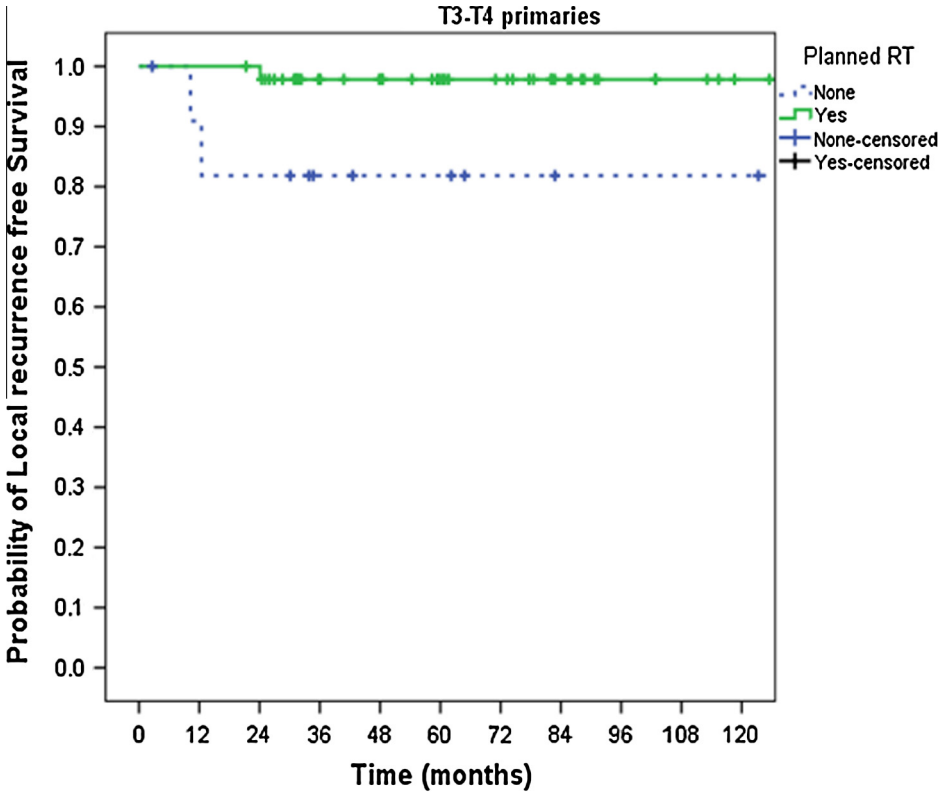

Fig. 3. Kaplan-Meier local recurrence-free survival in T3-T4 patients with and without primary bed radiation (log rank, p = 0.026).

disease-free after salvage chemoradiation; one died after palliative chemotherapy for unresectable recurrence in the parapharyngeal space; and one refused further treatment and died of progressive disease. None developed distant metastasis.

Discussion

In the T1-T2 primaries group, no significant association was observed between the oncologic outcomes and the presence or absence of postoperative primary bed radiation. The LR and LRFS rates of 3% and 98% respectively in patients who did not receive primary bed radiation are not significantly different from that of 0% and 94% in patients receiving planned primary bed radiation. However the functional outcome as assessed by the temporary gastrostomy rate differed significantly (6.5% versus 41%). The 95% CIs for ARR of LR crossed one, implying unknown benefit from primary bed radiation, however the ARI for a gastrostomy was 34.4% (95% CI: 24%, 45%). NNT to prevent a LR was higher than NNH for a gastrostomy (temporary or at two years). In the T3-T4 primaries group, primary bed radiation associated with a lower LR rate and higher LRFS. A higher gastrostomy rate was also observed. No definite conclusions about NNT and NNH could however be made since the 95% CIs crossed one.

Lack of adequate reporting of p16-positivity and stratification for T-classification in previous studies precludes comparison with our cohort. These previous observational studies have reported good local control with TOS alone for OPSCC [1,5]. In a cohort of 128 TLM-resected tonsil tumors, Hinni et al. [1] reported 100% local control in 40 previously untreated patients with surgery alone compared to 98% with surgery and adjuvant radiation. In a series of 69 patients treated with TLM alone, Grant et al. [5] reported local control of 90%, 94% and 100% for T1, T2 and T3 tumors respectively. In another series comparing 41 patients who received TLM alone versus 38 patients who received TLM and adjuvant therapy, Patel et al. [13] reported local control of 90% and 100% respectively. In the TLM alone group, the local control was 94% (n = 33/35) in the T1-T2 tumors and 66.7% (n = 4/6) in the T3-T4 tumors [13]. All local recurrences in the TLM alone group occurred in the presence of high-risk disease such as positive margin. Good local control rates have also been reported for early stage OPSCC undergoing TORS but rates specific for cohorts not receiving postoperative radiation are lacking [7,14,15].

Local control observed in our T1-T2 cohort without primary bed radiation was comparable to that of non-surgically treated OPSCC. Non-surgical OPSCC series in which early primaries constituted all or majority of the cases report LR rates between 5% and 7% and LRFS from 92% to 98% [16–19] but again, HPV status is not known. For instance, Garden et al. reported a LR rate of 7% in a cohort of 776 OPSCC patients (74%T1-T2) whereas Huang et al. reported it as 5% in a cohort of 442 (88%T1-T2) patients [16]. Advanced T-classification similar to our series was reported to correlate with higher LR [17]. In non-surgical studies which assessed HPV/p16-positivity, comparison of local recurrence rate with our study is prevented by reporting of "locoregional" recurrence instead of local recurrence as a separate outcome [20,21].

No significant difference in tracheostomy rates was noted between groups with or without primary bed postoperative radiation. Functional outcome when assessed by gastrostomy-tube rate differed between early and advanced primaries, as well as between patients with and without primary bed radiation within each group. In the T1-T2 group, the temporary gastrostomy rate was 6% for TOS alone and 42% for TOS with primary bed postoperative radiation. This resulted in ARI of 34% which dropped to 6% at two-year time point. Gastrostomy-tube rate has been used as a surrogate to assess the functional outcome of swallowing [22–25]. Worsening of swallowing with post-operative therapy is noted in TOS-resected OPSCC irrespective of the p16-status [7,24,26–28], and thus was an expected result in our study. When postoperative

radiation is administered after TOS resection, the primary bed has traditionally been included in the radiation field [29]. The extent of impact on swallowing from radiation to the oropharynx is shown to associate with the radiation dose and site in some studies, however there is a lack of consensus to date about the association [11,30–33]. Given the proximity to the lingual and palatine tonsils, the pharyngeal constrictors invariably receive high doses of radiation when the primary bed is irradiated [29] and dysphagia ensues.

Al-khudari et al. reported 0% versus 44% gastrostomy-tube rate for T1-T2 primaries without and with adjuvant treatment [34]. Although not specified, presumptively the majority of adjuvant treatment was administered to the primary bed. In a cohort of 34 OPSCC patients (97%T1-T2 and 74% p16-positive) treated with TORS alone, Choby et al. did not report any long-term gastrostomy usage [35]. In our T3-T4 group, the temporary gastrostomy-tube rate for patients without planned primary bed radiation was 33% versus 66% for patients receiving primary bed radiation. In non-surgical studies on OPSCC, gastrostomy rates ranging from 35% to 75% have been reported [17,19]. However, certain patients in these non-surgical studies, as seen in our advanced primaries group, may have received the gastrostomy-tube prophylactically, thus accounting for the high rates.

Being retrospective, this study is prone to selection bias and usual caution should be applied in the interpretation of the results; however, all consecutively-treated patients were assessed for their eligibility. The elimination of primary bed radiation was not performed *a priori* but the opportunity to assess its impact presented due to participation in institutional de-escalation initiatives or patient requirement. To address this limitation, heterogeneity of all study variables was carefully assessed between the groups of cases with and without planned primary bed radiation. There was no significant difference in proportion of patients within the two groups of cases with and without primary bed radiation (46% and 54%). Both groups were well-balanced (Table 1) for demographic, tumor and treatment attributes except for the variable of extracapsular extension (ECE). Lack of prognostication from ECE in p16-positive OPSCC has been demonstrated, however, in numerous studies [36,37]. In addition, the presence of ECE in ipsilateral neck may favor reduced local recurrence in the contiguous primary bed from the effects of higher nGTV radiation dose. Thus, greater frequency of ECE in the group receiving planned primary radiation versus a lower frequency in the group without planned primary radiation is unlikely to adversely impact the outcome of LR in the former group.

Another limitation could arise from lack of statistical power however the sample size could not be assessed due to absence of previous available studies. For future studies, we estimate that to detect a statistically significant LR rate difference of 3.2% in T1-T2 patients not receiving primary bed radiation versus those receiving it with 80% power at an alpha of 0.05, a total of 598 patients will be required with 299 in each arm. We also acknowledge that the primary tumor bed did receive a variable radiation dose in cases who received ipsilateral neck radiation. However, with IMRT, the dose would be exponentially decreasing from the lymphatic basin in the neck towards the midline. There may be other variables such as the specific resected pharyngeal structures which may have had a functional impact but were not accounted for even though the pathological T-classification of the primary site was obtained. And finally, we acknowledge the surrogate, approximate nature of gastrostomy rate as our functional metric for swallowing.

Our single-institution study may limit generalizability. However, in the absence of prospective data, observation of no significant association of primary bed radiation with LR and LRFS and a significantly increased gastrostomy rate in a large cohort of well-balanced groups of early T1-T2 primaries, with mature follow-up, proposes elimination of radiation to the primary bed for preservation of functional outcomes, without compromising oncologic outcomes. This is highly pertinent to planning of future adjuvant de-escalation trials in the TOS-resected p16-positive population.

Conclusions

Elimination of planned primary bed radiation in margin-negative resected, T1-T2 p16-positive OPC, did not associate with significant compromise in local control, but did associate with superior swallowing using gastrostomy tube as a surrogate. This, along with the 34% absolute risk increase for gastrostomy in T1-T2 patients radiated at the primary bed supports avoidance of planned radiation for prospective studies, and possibly for clinical practice. In T3-T4 tumors, planned primary adjuvant radiation associated with distinctly better local control which supports continued use in prospective studies and clinical practice.

Conflict of interest

Nothing to declare for all co-authors.

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