

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Radiotherapy techniques

Primary gross tumor volume (GTV) included all discernible gross disease appreciated on clinical examination, nasopharyngoscopy, imaging and operative and pathology reports. Primary nodal GTV included all proven or suspicious (>1 cm, necrotic, enhancing, or FDG avid) lymph nodes. The high risk clinical target volume (CTV_{59,4-60}) at the primary site was defined as GTV plus a margin of 1.0-cm to 1.5-cm. For OPC, in the node positive neck, CTV_{59,4-60} included levels II-IVa+b and retropharyngeal (RP) lymph nodes. In the node negative neck, CTV₅₄ included levels II-IVa and the RP nodes. For LRX, the high-risk clinical tumor volume (CTV_{59,4-60}) encompassed the supraglottic, glottic and subglottic larynx, as well bilateral cervical levels II-IV and level VIa. For HPX, the high-risk clinical tumor volume (CTV_{59,4-60}) margin around the GTV based on patterns of failure for the hypopharynx, including the bilateral RP nodes and levels II-IV. For OPC, LRX, and HPX, levels I and V were included when clinically involved or at risk. As data emerged over the course of the study period regarding low risk of cervical nodal failures in specific lymph node basins in OPC patients, we gradually removed these areas from our elective nodal volumes. These include level V (2009), level IB (2011) and higher retropharyngeal nodes in the uninvolved neck (2013)¹⁻⁴. Our current HNSCC target delineation practices have been previously described in detail⁵.

For OCC, details regarding delineation of target structures, total doses, and dose per fraction specifications used at MSKCC have been previously described in detail⁶. The CTV₆₀₋₆₆ included the post-operative bed within the oral cavity. If margins were positive or close, the dose was increased to 66 Gy. The involved neck was included in the CTV₆₀₋₆₆ with areas of pathologic extranodal extension boosted to 66 Gy. The contralateral uninvolved neck was included in the CTV₅₄. PTV margin expansions were the same as used for definitive IMRT cases. In the presence of gross disease, The PTV₇₀ was defined as the CTV₇₀ plus a margin of 0.3-cm to 0.5-cm, and the PTV_{59,4-60} and PTV₅₄ were defined as their respective CTVs plus an identical margin range.

In the definitive setting, dose was prescribed in one of two ways: either with 2.12 Gy, 1.8 Gy, and 1.64 Gy daily fractions over a course of 33 days to the PTV₇₀, PTV_{59,4}, and PTV₅₄, respectively, or with a cone-down technique with 2 Gy daily fractions to PTV₇₀ and PTV₆₀ and 1.8 Gy daily fractions to PTV₅₄ for 30 days followed by 5 additional 2 Gy fractions to PTV₇₀. The lower neck was either included in the IMRT fields or included in a low anterior neck field matched to the IMRT fields. Treatment planning was performed using an in-house treatment planning software.

Regional nodal failure mapping

Regional nodal failures were delineated on diagnostic imaging and co-registered with the original treatment planning CT. The failure was classified as in-field, marginal or out-of-field based on the relative volumes of the recurrent nodes covered by the 95% prescription isodose region in the original treatment plan. In-field was defined as 95% of the lesion within the 95% isodose, marginal as 20-95% within the 95% isodose and out-

of-field as <20% within the 95% isodose. This classification was used for GTV dose levels (70 Gy) as well as CTV dose levels (54-66 Gy). In this way, recurrences were defined as in-field GTV, in-field CTV, marginal or out-of-field. The distributions of the recurrent nodes were then documented according to the cervical nodal levels. In cases of recurrence spanning multiple cervical nodal levels, the recurrence was enumerated for each involved level.

Salvage treatment

Locoregional salvage treatment following locoregional recurrence was documented for each case. Salvage surgery was defined as excision of recurrent disease with definitive or palliative intent including resection of disease at the primary site of local failure and/or cervical neck dissection of any kind. The decision to undergo salvage surgery was based on the decision of the multidisciplinary team. Reasons for not undergoing salvage surgery include synchronous distant metastasis, unresectable disease, poor performance status and patient refusal. Salvage re-irradiation was defined as the administration of a second course of radiation to a previously treated recurrent site as part of a treatment regimen with definitive or palliative intent. Salvage radiation treatment modalities included photon IMRT, proton therapy, brachytherapy or intraoperative radiation. For patients who received fractionated photon or proton re-irradiation, treatment was performed +/- concurrent radiosensitizing chemotherapy.

eTable 1. Baseline Characteristics

	Oropharynx	Oral cavity	Larynx	Hypopharynx
N	703	125	126	46
Age				
Median	57	62	63	64
Range	25-91	20-92	34-89	47-91
Gender				
Male	616 (88)	74 (59)	86 (68)	38 (83)
Female	87 (12)	51 (41)	40 (32)	8 (17)
KPS				
Median	90	90	90	90
Range	60-100	50-100	60-100	70-100
p16/HPV Status				
Positive	334 (48)			
Negative	66 (9)			
Unknown	303 (43)			
T classification				
T1	188 (27)	24 (19)	8 (6)	9 (20)
T2	298 (42)	40 (32)	24 (19)	12 (26)
T3	132 (19)	8 (6)	71 (56)	17(37)
T4	85 (12)	53 (42)	23 (18)	8 (17)
N classification				
N0	27 (4)	21 (17)	48 (38)	4 (9)
N1	127 (18)	36 (29)	22 (17)	10 (22)
N2	532 (76)	68 (54)	52 (41)	27 (59)
N3	17 (2)	0 (0)	4 (3)	5 (11)

Stage (AJCC)				
III	129 (18)	36 (29)	57 (45)	12 (26)
IV	574 (82)	89 (71)	69 (55)	34 (74)
Concurrent Systemic therapy				
3-weekly cisplatin	454 (65)	29 (23)	87 (69)	27 (59)
Weekly cisplatin	9 (1)	8 (6)	9 (7)	1 (2)
Cetuximab	82 (12)	6 (5)	9 (7)	4 (9)
Carbo + 5-FU	51 (7)	4 (3)	9 (7)	4 (9)
Cisplatin + bev	39 (6)	0 (0)	0 (0)	0 (0)
Carbo + paclitaxel	27 (4)	4 (3)	6 (5)	7 (15)
Other	28 (4)	0 (0)	4 (3)	0 (0)
None	13 (2)	74 (59)	2 (2)	3 (7)

KPS=Karnofsky performance status, HPV=human papillomavirus.

eTable 2. Patient Characteristics at the Time of Recurrence

	Locoregional failure	Distant failure
N	147	143
Gender		
Male	116 (79%)	118 (83%)
Female	31 (21%)	25 (17%)
Age at progression (median, range)	63 (34-92)	61 (28-88)
KPS at progression (median, range)	90 (50-100)	80 (40-100)
Subsite		
Oropharynx	71 (48%)	87 (61%)
HPV/p16+	29 (20%)	42 (48%)
HPV/p16-	19 (13%)	15 (17%)
HPV/p16 unknown	23 (16%)	30 (34%)
Oral cavity	35 (24%)	19 (13%)
Larynx	27 (18%)	23 (16%)
Hypopharynx	14 (10%)	56 (39%)

KPS=Karnofsky performance status.

eTable 3. Locations of Regional Nodal Failures in Relation to IMRT Treatment Fields Across Disease Subsites

	In-field GTV	In-field CTV	In-field GTV and CTV	In-field GTV/CTV and Out-of-field	Marginal	Out of field only
Oropharynx	34 (4.8%)	6 (0.8%)	4 (0.6%)	0 (0%)	0 (0%)	0 (0%)
HPV/p16-	8 (12.1%)	0	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)
HPV/p16+	16 (4.8%)	4 (1.2%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)
HPV/p16 unknown	10 (3.3%)	2 (0.7%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Larynx	5 (4.0%)	1 (0.8%)	5 (4.0%)	1 (0.8%)	0 (0%)	0 (0%)
Hypopharynx	4 (8.7%)	1 (2.2%)	2 (4.3%)	0 (0%)	0 (0%)	0 (0%)
Total Non-oral cavity (definitive IMRT)	43 (4.9%)	8 (0.9%)	11 (1.3%)	1 (0.1%)	0 (0%)	0 (0%)
Oral cavity	NA	12 (9.6%)*	NA	3 (2.4%)	0 (0%)	0 (0%)

GTV=gross tumor volume, CTV=clinical tumor volume, HPV=human papillomavirus, IMRT=intensity modulated radiation therapy. *Of 12 In-field CTV failures in oral cavity cases, 7 occurred outside of areas of prior gross disease, 2 occurred in areas of prior gross disease and 3 failed in both areas of gross disease and outside.

eTable 4. Oral Cavity Regional Nodal Failures and Relationship to Neck Dissection

Oral cavity regional nodal failures (n=15)		
Neck dissection	None	0 (0%)
	Unilateral	15 (100%)
	Bilateral	0 (0%)
N-stage	pN0	2 (13%)
	pN1	2 (13%)
	pN2a	0 (0%)
	pN2b	11 (73%)
	pN2c	0 (0%)
	pN3	0 (0%)
Location of recurrent nodes relative to neck dissection	In dissected region	3 (20%)
	Contralateral	9 (60%)
	Both ipsilateral and contralateral	3 (20%)

All patients with recurrent regional nodes had undergone unilateral neck dissection. The majority of failures involved recurrence contralateral to the dissected region.

eTable 5. First Organs of Distant Metastasis Across HNSCC Subsites

	Oropharynx			Oral cavity (N=19)	Larynx (N=23)	Hypopharynx (N=14)	Total (N=143)
	HPV/p16+ (N=42)	HPV/p16- (N=15)	HPV/p16 unknown (N=30)				
Lung	31 (74%)	11 (73%)	27 (90%)	17 (89%)	21 (91%)	7 (50%)	114 (80%)
Lymph node (below clavicles)	15 (36%)	5 (33%)	15 (50%)	7 (37%)	9 (39%)	6 (43%)	57 (40%)
Brain	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Liver	3 (7%)	1 (7%)	6 (20%)	0 (0%)	1 (4%)	2 (14%)	13 (9%)
Skin	1 (2%)	0 (0%)	0 (0%)	1 (5%)	1 (4%)	0 (0%)	3 (2%)
Kidney	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (1%)
Bone	7 (17%)	2 (13%)	8 (27%)	4 (21%)	4 (17%)	3 (21%)	28 (20%)
Soft tissue	3 (7%)	1 (7%)	2 (7%)	0 (0%)	2 (9%)	1 (7%)	9 (6%)
Bowel	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	2 (1%)
Heart	0 (0%)	0 (0%)	0 (0%)	1 (53%)	0 (0%)	1 (7%)	2 (1%)
Adrenal	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)

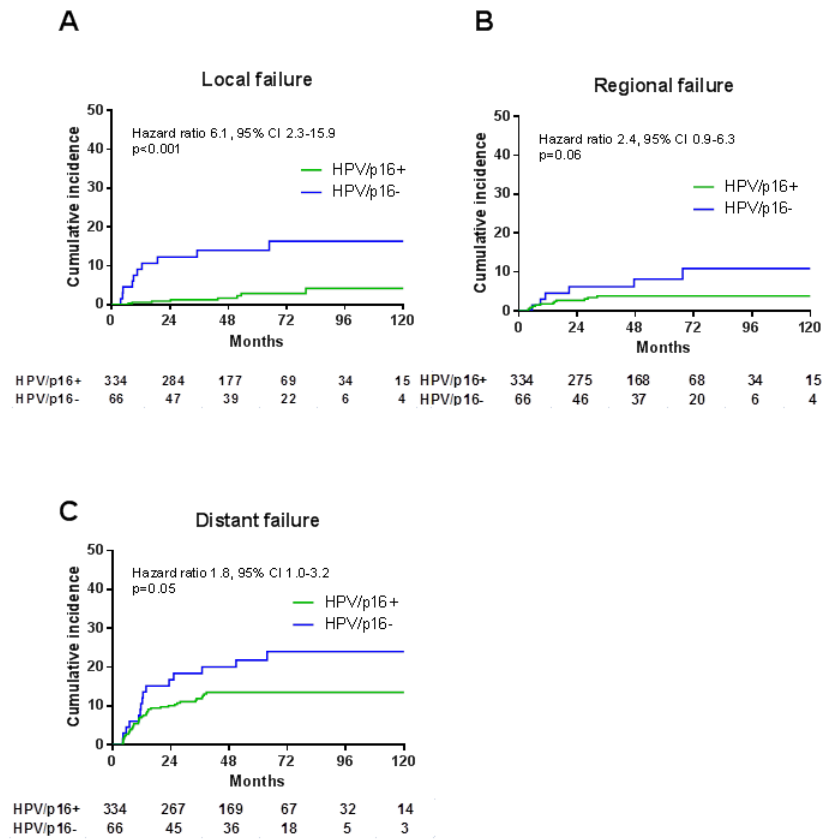
HPV=human papillomavirus.

eTable 6. Burden of Metastatic Disease Across Head and Neck Squamous Cell

Carcinoma Subsites

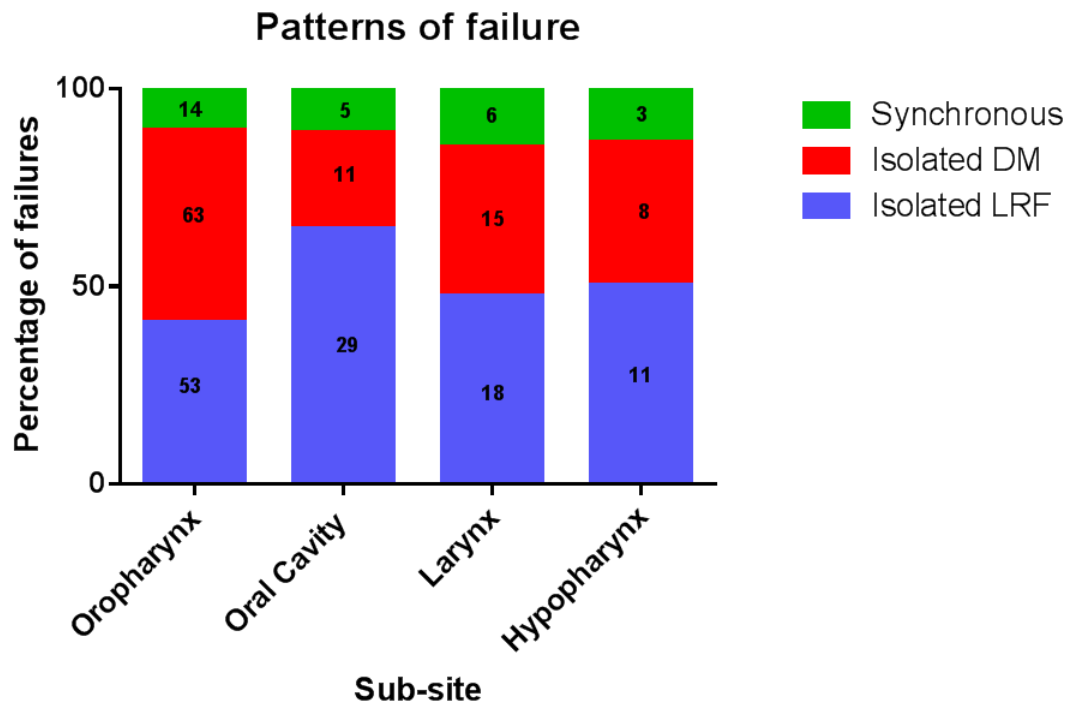
# of metastases	N	OPC	HPV/p16+ OPC	HPV/p16- OPC	HPV/p16 unknown OPC	OCC	LRX	HPX
1	19	12 (63%)	7 (37%)	3 (16%)	2 (11%)	4 (21%)	2 (11%)	1 (5%)
2-4	64	47 (73%)	23 (36%)	9 (14%)	15 (23%)	7 (11%)	7 (11%)	3 (5%)
5	60	28 (5%)	12 (20%)	3 (5%)	13 (22%)	8 (13%)	14 (23%)	10 (17%)

eFigure 1. Cumulative Incidence of (A) Local, (B) Regional and (C) Distant Failure in HPV/p16+ vs HPV/p16- Oropharyngeal Squamous Cell Carcinoma



HPV=human papillomavirus.

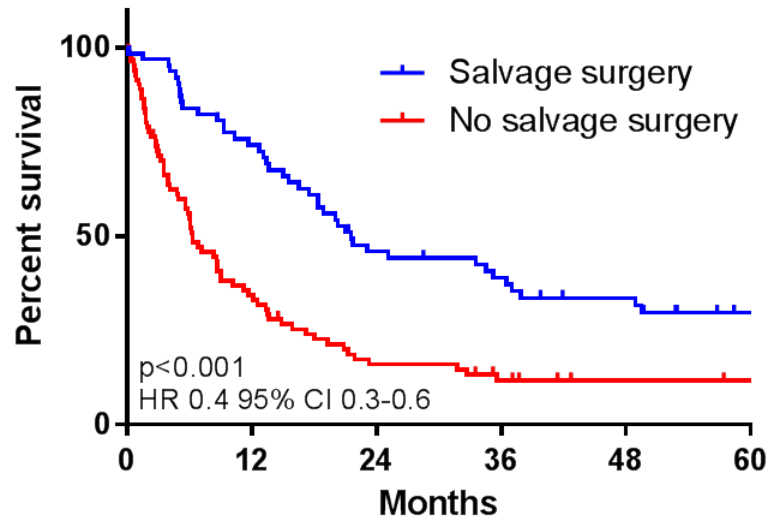
eFigure 2. Patterns of Failure Across Subsites



DM=distant metastasis, LRF=locoregional failure.

eFigure 3. Survival Following Locoregional Recurrence According to Receipt of Salvage Surgery

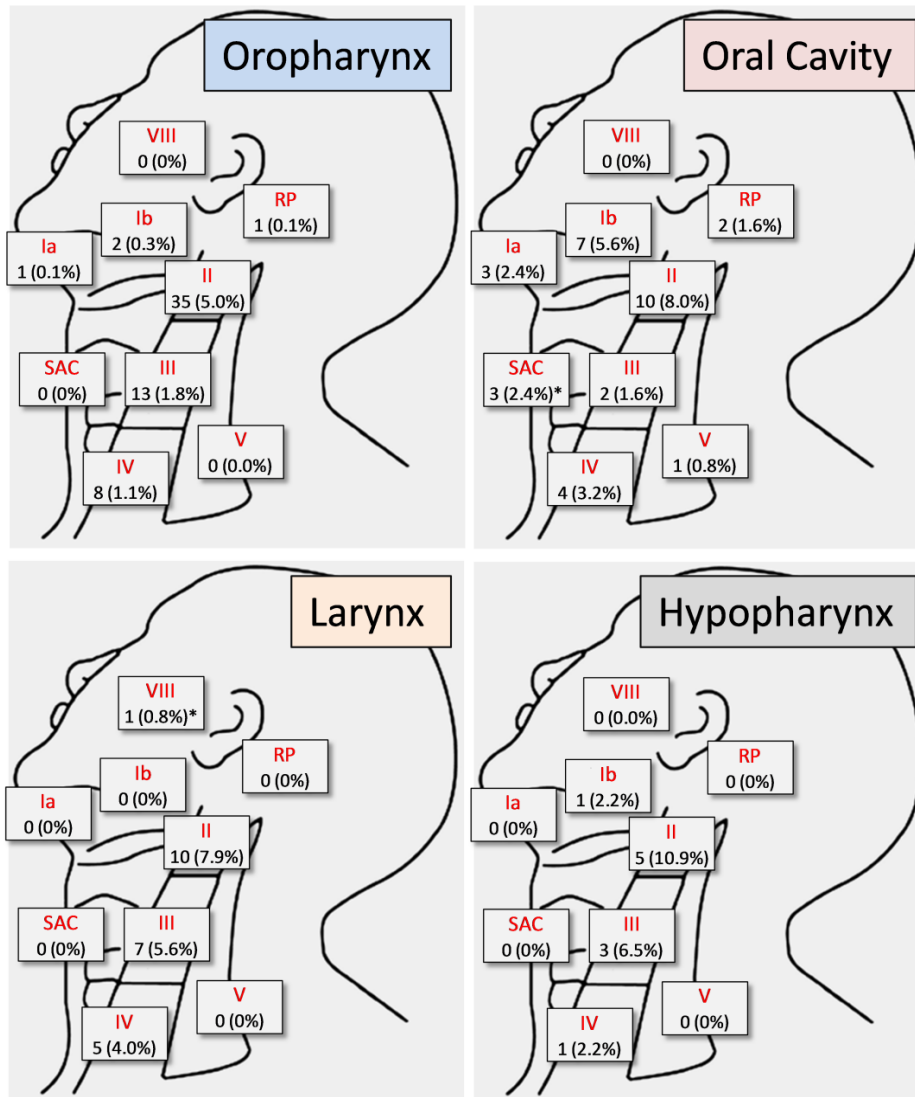
Survival following locoregional recurrence



Salvage surgery	64	46	28	23	18	11
No salvage surgery	83	28	13	8	4	3

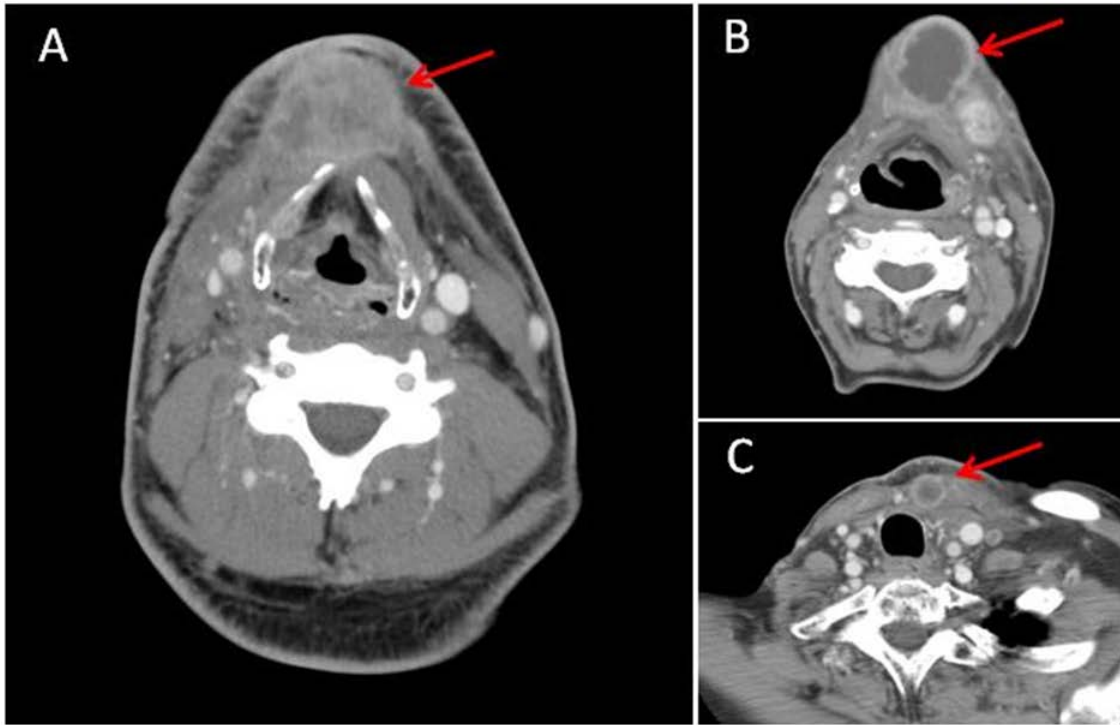
HR=hazard ratio, CI=confidence interval.

eFigure 4. Patterns of Regional Nodal Failure Across Head and Neck Squamous Cell Carcinoma Subsites



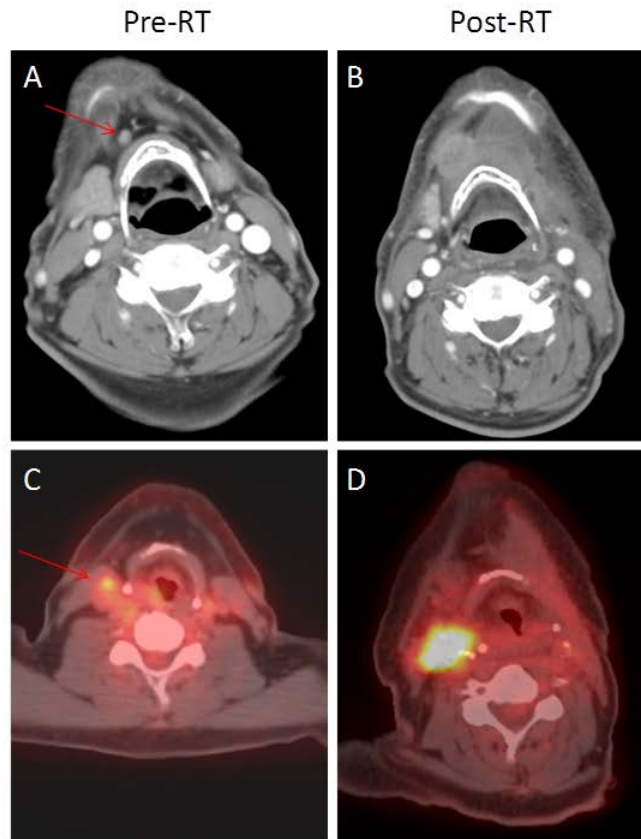
Failures that occurred outside of the radiation field are indicated with *. All other failures occurred within the radiation field, no marginal failures were observed. SAC=superficial anterior cervical lymph nodes, RP=retropharyngeal lymph nodes.

eFigure 5. Examples of Out-of-Field Superficial Anterior Cervical Node Failures in Patients With Oral Cavity Squamous Cell Carcinoma Following Postoperative Intensity Modulated Radiation Therapy



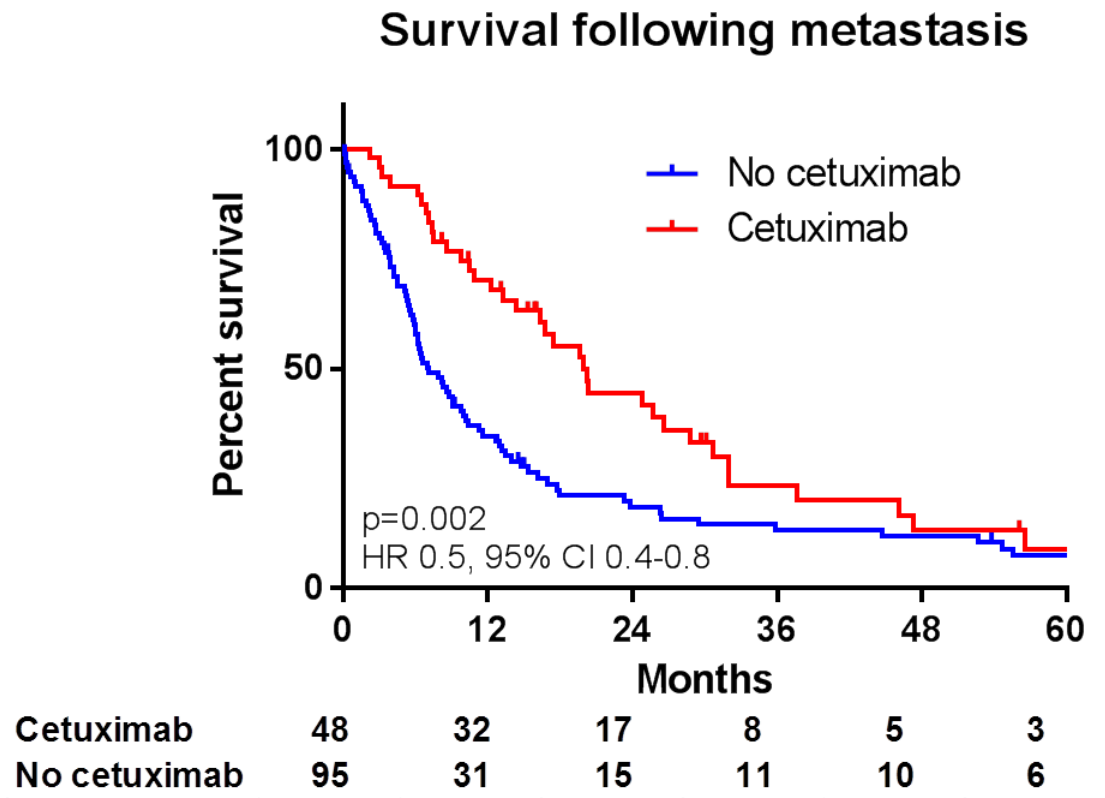
(B) and (C) demonstrate the same patient.

eFigure 6. Examples of Regional Failures Contralateral to the Dissected Neck in Oral Cavity Patients Treated With Postoperative IMRT



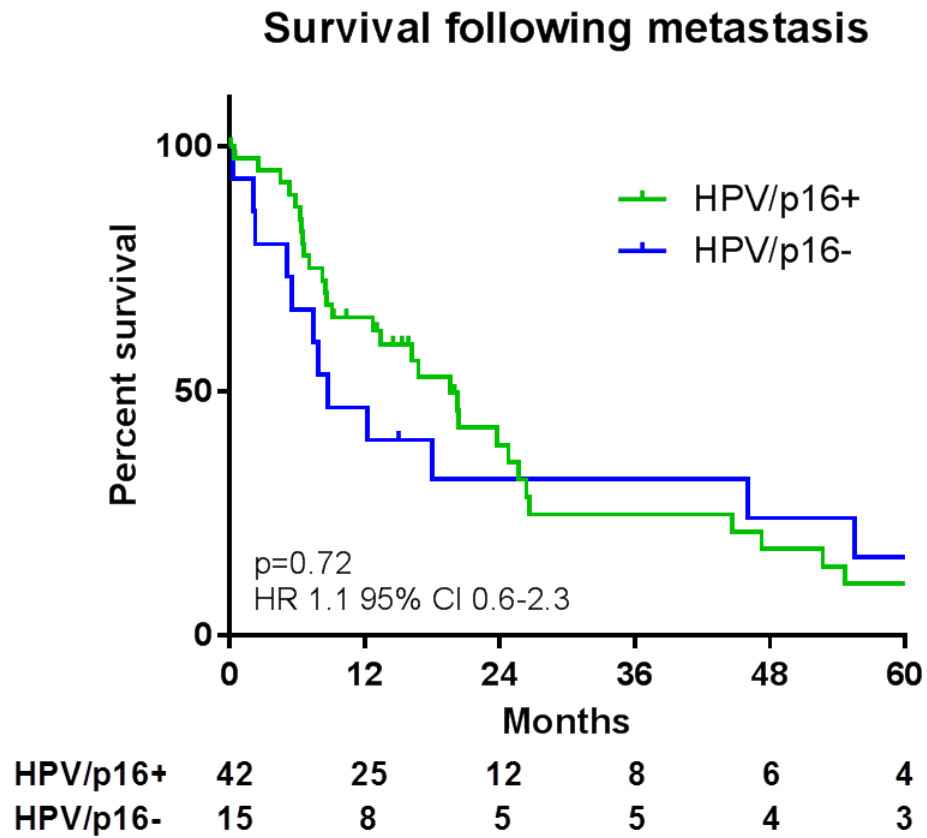
A 66 year old man with pT2N2b squamous cell carcinoma of the buccal mucosa underwent resection and left modified radical neck dissection. A small right level Ib node was present (A) post-operatively. Recurrence developed at this site 4 months following cetuximab-IMRT (B). A 65 year old man with pT4aN2b SCC of the left oral tongue underwent resection with left modified radical neck dissection. Post-operative imaging revealed a mildly avid right level III node (C). Recurrence developed at this site 10 months following cisplatin-IMRT (D).

eFigure 7. Survival Following Metastasis According to Receipt of Palliative Systemic Therapy Regimen Containing Cetuximab



HR=Hazard ratio, CI=Confidence interval.

eFigure 8. Survival Following Distant Metastasis According to Human Papillomavirus (HPV)/p16 Status



HR=Hazard ratio, CI=Confidence interval.

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