Hypoxia-Directed Treatment of Human Papillomavirus–Related Oropharyngeal Carcinoma

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ABSTRACT

PURPOSE Standard curative-intent chemoradiotherapy for human papillomavirus (HPV)–related oropharyngeal carcinoma results in significant toxicity. Since hypoxic tumors are radioresistant, we posited that the aerobic state of a tumor could identify patients eligible for de-escalation of chemoradiotherapy while maintaining treatment efficacy.

METHODS We enrolled patients with HPV-related oropharyngeal carcinoma to receive de-escalated definitive chemoradiotherapy in a phase II study (ClinicalTrials.gov identifier: NCT03323463). Patients first underwent surgical removal of disease at their primary site, but not of gross disease in the neck. A baseline ^{18}F-fluoromisonidazole positron emission tomography scan was used to measure tumor hypoxia and was repeated 1-2 weeks intratreatment. Patients with nonhypoxic tumors received 30 Gy (3 weeks) with chemotherapy, whereas those with hypoxic tumors received standard chemoradiotherapy to 70 Gy (7 weeks). The primary objective was achieving a 2-year locoregional control (LRC) of 95% with a 7% noninferiority margin.

RESULTS One hundred fifty-eight patients with T0-2/N1-N2c were enrolled, of which 152 patients were eligible for analyses. Of these, 128 patients met criteria for 30 Gy and 24 patients received 70 Gy. The 2-year LRC was 94.7% (95% CI, 89.8 to 97.7), meeting our primary objective. With a median follow-up time of 38.3 (range, 22.1-58.4) months, the 2-year progression-free survival (PFS) and overall survival (OS) rates were 94% and 100%, respectively, for the 30-Gy cohort. The 70-Gy cohort had similar 2-year PFS and OS rates at 96% and 96%, respectively. Acute grade 3-4 adverse events were more common in 70 Gy versus 30 Gy (58.3% *v* 32%; $P = .02$). Late grade 3-4 adverse events only occurred in the 70-Gy cohort, in which 4.5% complained of late dysphagia.

CONCLUSION Tumor hypoxia is a promising approach to direct dosing of curative-intent chemoradiotherapy for HPV-related carcinomas with preserved efficacy and substantially reduced toxicity that requires further investigation.

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INTRODUCTION

Human papillomavirus (HPV)–related oropharyngeal cancers are distinct from tobacco-related cancers and constitute one of the most common head and neck cancers in the United States.[1] Definitive chemoradiotherapy or surgery followed by postoperative radiotherapy with or without chemotherapy are two standard treatments.[2] While HPV-related oropharyngeal cancers have favorable oncologic outcomes after standard therapy, patients experience long-term side effects, that is, dysphagia and dental complications.[3,4] These toxicities have prompted various de-escalation strategies aimed at reducing morbidity.[5] Unfortunately, phase III studies substituting cisplatin with cetuximab failed to decrease toxicity and, in fact, demonstrated worse oncologic outcomes.[3,4,6] Similarly, phase II studies involving accelerated radiation,

CONTEXT

Key Objective

Numerous phase II clinical trials have investigated disease control outcomes in patients with human papillomavirus (HPV)–positive cancers when treated with various de-escalation strategies, but high-dose cisplatin concomitant with 70 Gy radiation remains the standard of care. Chemoradiotherapy is highly effective but associated with significant acute and long-term toxicities.

A phase II clinical trial was designed to investigate an hypothesis that measurement of tumor hypoxia with ^{18}F-fluoromisonidazole (FMISO) positron emission tomography (PET) could identify patients eligible for de-escalation from standard 70 Gy to 30 Gy.

Knowledge Generated

Of the 152 eligible patients, 128 received 30 Gy. The 2-year locoregional control and overall survival rates were 94.7% and 100%, respectively. FMISO PET may be able to identify HPV-related oropharyngeal cancers that can receive significant de-escalation of chemoradiotherapy.

Relevance *(M.L. Gillison)*

Although disease control rates appear promising for patients without baseline or early on treatment hypoxia treated with 30 Gy, this approach remains investigational and warrants prospective comparison to the standard of care.*

*Relevance section written by *JCO* Associate Editor Maura L. Gillison, MD.

induction or concurrent de-escalated chemoradiotherapy, or surgical de-escalation have modest toxicity reductions from standard chemoradiation and some had inferior oncologic outcomes.[5,7–14] The outcome differences in these trials could be attributed to de-escalated therapy on the basis of only traditional clinical features.

Tumor hypoxia diminishes the effectiveness of chemoradiotherapy by reducing radiation-induced free radical production, leading to decreased DNA damage. Consequently, tumor hypoxia is associated with poor outcomes after radiotherapy[15,16] and might explain why some tumors require a higher dose of radiation for locoregional control (LRC).[17–19] Hypoxia has been measured clinically using ^{18}F-fluoromisonidazole (FMISO) positron emission tomography (PET)[20] and associated with poor outcomes in head and neck cancer by multiple groups.[18,21,22] Interestingly, baseline levels of hypoxia measured by FMISO PET are similar in HPV-related and HPV-negative tumors.[23] Although the majority of hypoxia work has involved HPV-negative disease,[18,19,21] emerging evidence suggests that it may also be prognostically important in HPV-related oropharyngeal cancers as well.[24,25] Swartz et al[24] identified that hypoxia measured by HIF-1α immunohistochemistry in HPV-related oropharyngeal carcinoma decreases overall survival. Furthermore, an individual patient meta-analysis of hypoxia imaging suggests that it may be associated with worse outcomes in HPV-related cancers, albeit with a small number of patients.[25]

Given hypoxia's role in mediating radiation resistance and its association with outcomes in HPV-related oropharyngeal carcinoma,[24,25] we hypothesized that tumors without hypoxia can be treated with a significantly lower radiation dose. We conducted a pilot study[26] in 19 patients with HPV-related oropharyngeal cancer who underwent surgical removal of their primary tumor followed by de-escalated chemoradiotherapy to gross nodal disease. Tumors without hypoxia on FMISO PET were de-escalated to 30 Gy, a curative dose traditionally used for HPV-related anal cancers.[27] All de-escalated patients had a planned neck dissection at 4 months post-treatment, and 87% were observed to have a major pathologic response (<10% viable tumor).

On the basis of these data and the unmet need to reduce toxicity while maintaining efficacy, we conducted a phase II study personalizing HPV-related oropharyngeal cancer treatment by using FMISO PET. We evaluated the efficacy of 30 Gy in controlling gross nodes in the neck, without a planned neck dissection. However, given the radical radiation dose reduction, the difficulty in salvaging primary tumors, and the desire to conduct de-escalation trials in a stepwise manner, we continued to incorporate surgical removal of the primary site for this protocol.

METHODS

Study Design

The study was designed, sponsored by the Memorial Sloan Kettering Cancer Center, and approved by its institutional review board (ClinicalTrials.gov identifier: NCT03323463, cohort A). Between October 2017 and December 2020, patients were consented, enrolled, and treated at seven different locations within our network. Eligible patients were 18 years and older; had HPV-related oropharyngeal cancer (tonsil, base of

tongue, unknown primary), Eastern Cooperative Oncology Group 0-2, and clinical stage T0-2/N1-2c/M0 (American Joint Committee on Cancer, seventh edition); and were able to receive high-dose cisplatin or carboplatin/5-fluorouracil (5FU). HPV status was determined by either positive p16 expression (70% nuclear and cytoplasm expression; Ventana Medical Systems) or mRNA HPV in situ hybridization (RNAscope 2.5 HD Reagent kit [Advanced Cell Diagnostics, Inc, Hayward, CA]).

Before starting chemoradiotherapy, patients underwent primary tumor resection (T1, T2) using a method at the discretion of the surgeon including but not limited to robotic surgery. Microscopic positive margins were permitted. All patients had intact gross nodal disease. Radiation planning occurred approximately 3 weeks postsurgery (median, 2.76 weeks [range, 0.56-3.43 weeks]). FDG PET/computed tomography (CT) radiation simulation, diagnostic magnetic resonance imaging (MRI), and/or CT scans were performed followed by a FMISO PET. Patients with baseline hypoxia underwent repeated FMISO PET 1-2 weeks intratreatment. Only one baseline FMISO PET was performed given its excellent reproducibility on the basis of our previous work.[20] Hypoxia status was determined by our established highly reproducible hybrid method on the basis of both a qualitative binary assessment of four standardized image characteristics and a quantitative tumor to background ratio (TBR) on late (150 minutes postinjection) static PET images.[28] Typically, there was agreement between the qualitative and quantitative interpretations for the positive scans when using the previous recommended ratio of >1.3, but when there was a disagreement, the visual assessment prevailed (Fig 1A; Data Supplement, Methods [online only]). Pharmacokinetic modeling of dynamic FMISO PET was also performed (Data Supplement, Methods).

Personalized Chemoradiotherapy and Follow-Up

Patients without hypoxia on their baseline FMISO PET scan and patients who had hypoxia resolution on their intratreatment FMISO PET received a total dose of 30 Gy at 2 Gy/fraction/d. Patients also received concurrent chemotherapy with two cycles of cisplatin 100 mg/m^2 or two cycles carboplatin AUC of 5 and 5FU of 2,400 mg/m^2 over 4 days, given on weeks 1 and 4 (second cycle after radiation therapy completion; Fig 1A; Data Supplement, Table 1). All patients received IMRT, targeting the postoperative primary site, gross neck nodes, and potential areas of microscopic spread (typically bilateral necks), all uniformly receiving 30 Gy. For tonsil cancers, the ipsilateral pterygoid plate was included, whereas the pre-epiglottic space was included for base of tongue cancers. Primary site margin did not influence radiotherapy dosing. Well-lateralized tonsil cancer with a single gross node received ipsilateral radiation. For unknown primary cases, the entire oropharyngeal axis was treated. These patients also had a full workup including ipsilateral tonsillectomies. Patients whose tumors exhibited persistent hypoxia on intratreatment FMISO PET received a boost of 40 Gy/2 Gy/fraction to gross nodal disease to a total of 70 Gy with chemotherapy (Figs 1A and 1C). Each patient had two plans: a plan to 30 Gy and a subsequent cone-down plan to 70 Gy. If the patient had hypoxia resolution, the 70 Gy plan was not delivered. Departmental guidelines on radiation target delineations and planning guidelines were followed and reviewed by two radiation oncologists (N.Y.L. and N.R.).

Additional once weekly MRIs and blood samplings were performed. Standard surveillance was performed but in addition included PET, MRI, and/or CT scans at 3-4 months and 1 and 2 years post-treatment.[2]

Primary and Secondary End Points

The primary end point was 2-year LRC for patients treated with personalized chemoradiotherapy on the basis of FMISO PET. Locoregional failure was defined as any recurrence at the primary tumor site at any time or a neck recurrence >140 days from the end of chemoradiation using definitions adopted from NRG Oncology.[3,9] Recurrence was confirmed pathologically. Secondary end points were distant metastasis (DM), progression-free survival (PFS), overall survival (OS), and patient-reported quality-of-life (PRO) outcomes. Acute/late toxicities were assessed by using National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0 from the start of all therapies. PROs were collected using MD Anderson Dysphagia Inventory,[29] European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire,[30] and Financial Toxicity (COST-FACIT) surveys.[31] Objective speech/swallowing function assessments were performed with a modified barium swallow (Data Supplement, Methods). Correlative biomarkers included pretreatment and weekly intratreatment diffusion-weighted (DW) MRIs; tumor-informed assay was performed to assess cell-free circulating tumor DNA (ctDNA) in blood samples obtained before and 2 weeks into chemoradiation (Data Supplement, Methods). As a proxy for cost, we priced the hospital/physician services used by the patients at Medicare service fee rates.

Statistical Analysis

Our primary objective was to determine if the 2-year LRC was comparable with our historical control of 95% with standard chemoradiotherapy,[3,4] with a 7% noninferiority margin. To allow for 5% attrition, we enrolled 158 patients where the primary end point was based on the first 150 eligible patients and secondary end points included all eligible patients. A prespecified statistical analysis plan was developed using a one-sided one-sample proportion test for the hypotheses H_0: $P \leq 88\%$ versus H_1: $P > 88\%$, where P represents the 2-year LRC. With 150 patients, we had a >0.85 power for detecting whether personalized chemoradiation on the basis of the FMISO PET results would result in a 2-year LRC of 95% with an alpha of .025. Secondary end points included Kaplan-Meier estimates to assess PFS and OS, whereas cumulative incidence functions were used to assess DM and LRC. Acute/late toxicities and PRO

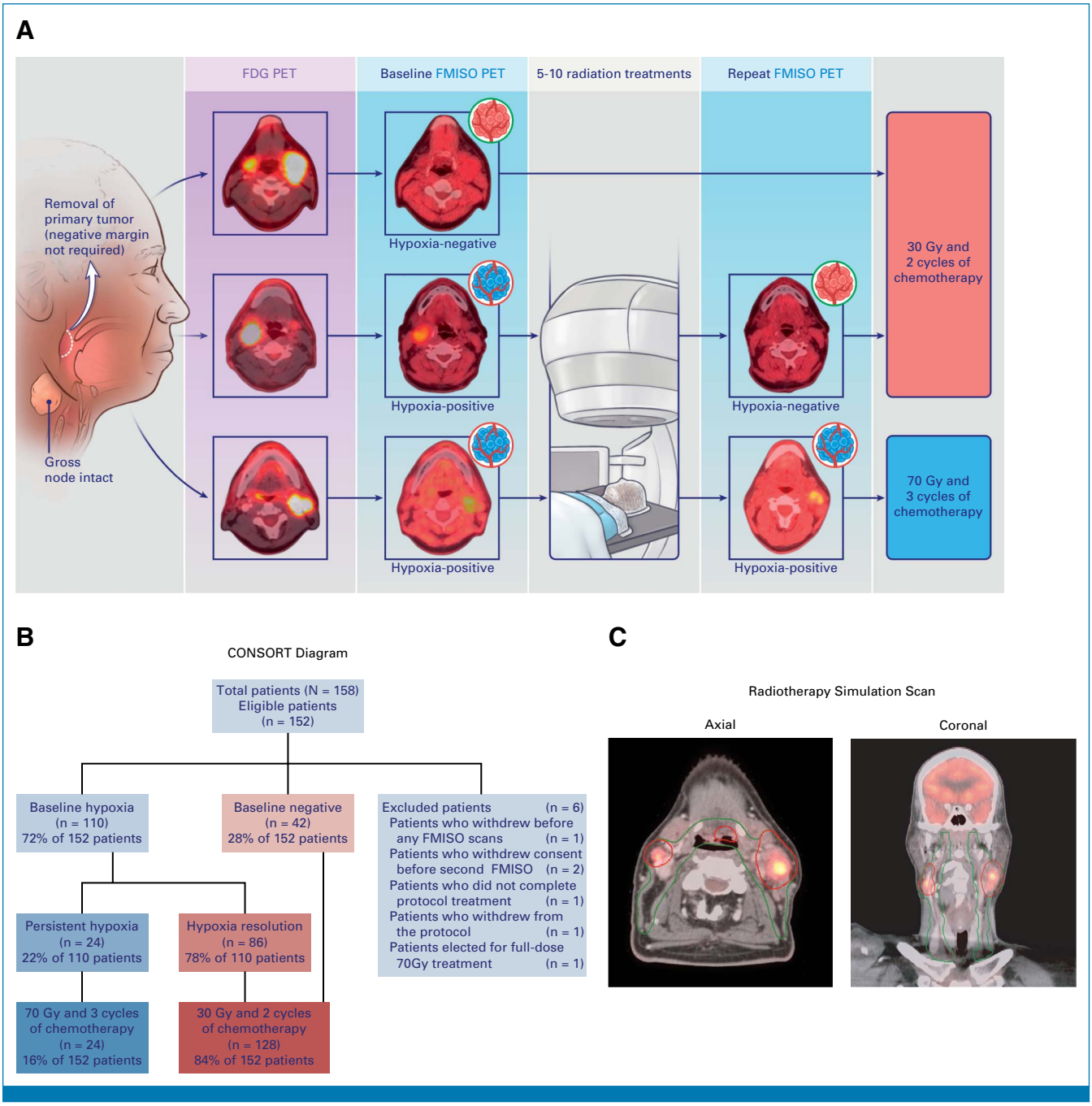

FIG 1. A phase II clinical trial of personalized radiotherapy for oropharyngeal cancer (30-ROC). (A) Protocol schema illustrating typical positive and negative FMISO PET scans pre- and repeated intratreatment along with which patients received 30 Gy versus 70 Gy. (B) CONSORT diagram of all enrolled patients (n = 158), illustrating excluded patients (n = 6) and aggregate statistics for FMISO PET pre- and repeated intratreatment results. (C) Radiotherapy volumes (PTVs) for a typical case on study in a patient with a T1N2c base of tongue tumor. Note that the green contour is PTV that targets microscopic disease and receives 30 Gy regardless of hypoxia status. Red contour highlighting gross nodal disease will receive 30 or 70 Gy depending on hypoxia status. FDG PET, fluorodeoxyglucose positron emission tomography; FMISO PET, 18F-fluoromisonidazole positron emission tomography; PTV, planning target volume; ROC, reduction in oropharyngeal carcinoma.

scores with the specified time points were tabulated/summarized. The exploratory objectives involved correlation analyses of binary factors (ie, ctDNA detection using Fischer's exact test) and continuous variables (ie, volume and mean ADCs derived from DW-MRI using the Wilcoxon rank-sum test) to identify candidates for de-escalated therapy.

RESULTS

Patients

One hundred fifty-two patients were eligible for analysis (Fig 1B). Clinical characteristics are presented in Table 1.

Baseline FMISO PET scans were positive in 110 (72%) patients (median TBR, 1.6 [range, 0.82-3.43]) and negative in 42 (28%) patients (median TBR, 0.97 [range 0.69-1.31]; Appendix Table A1). Of the 110 patients with pretreatment tumor hypoxia, 86 eventually showed hypoxia resolution on repeat intratreatment FMISO PET (TBR, 1.0 [range, 0.63-1.33]). Thus, 24 (16%) patients had nodal disease with persistent hypoxia (median TBR, 1.32 [range, 0.94-2.00]) and treated with 70 Gy, whereas the other 128 (84%) patients received 30 Gy. Of the 128 de-escalated patients, only three were selected as negative on the basis of visual assessment of FMISO-PET despite a TBR of >1.3. The median TBR of 30 Gy patients was lower than that of 70 Gy patients (Data Supplement, Fig S1A, online only). Compartmental analysis from dynamic PET was consistent with TBR derived from late, static FMISO PET images (Data Supplement, Figs S1B and S1C).

Clinical characteristics were not significantly associated with baseline hypoxia status (Data Supplement, Table S1). There was no difference in baseline hypoxia status among never smokers, ≤10 pack-year smokers, and >10 pack-year smokers, and six were current smokers. Smokers were three times more likely to have persistent hypoxia during therapy versus never smokers (P = .02; Data Supplement, Table S1). Among the 128 de-escalated patients, 110 patients initially received two cycles of cisplatin and 18 received carboplatin/5FU. All patients received chemoradiation per protocol.

Efficacy

At the time of data cutoff, the median follow-up was 38.3 months (range, 22.1-58.4 months). The study met its primary objective with a 2-year LRC of 94.7% (CI, 89.8 to 97.7; Fig 2A). The 2-year PFS and OS rates for the entire study were 94% and 99%, respectively. The 2-year PFS and OS were 94% and 100% for the 30-Gy cohort and 96% and 96% for the 70-Gy cohort (Figs 2B and 2C), respectively. There was one death from pulmonary embolus in the 70-Gy cohort. Despite an approximately 60% radiation dose reduction, only eight patients had nodal recurrences (median, 8.1 months [range, 6.8-22.4 months]); all underwent successful limited neck dissections. Four patients had persistent nodal disease for <140 days (Data Supplement, Table S10). No 70 Gy patients experienced a nodal failure. No patients failed in the primary site nor a primary emerged in patients who presented with carcinoma of unknown primary. A single patient in the 30-Gy cohort developed DM. The 2-year disease-specific survival for the entire cohort was 100%. There were no associations between clinical factors and the probability of locoregional recurrence (Data Supplement, Table S2).

Adverse Events

Across both cohorts, for ≥grade 3 acute toxicities, <9% of patients had radiation-related and <55% had chemotherapy-related. For late ≥grade 3 toxicities, <0.7% of the patients had radiation-related and none had chemotherapy-related (Data Supplement, Table S3). Fifty-six percent of patients did not require narcotics for pain relief. Regarding late toxicities in the entire cohort, we observed 2.6% grade 2 xerostomia, 5.2% grade 2 dysgeusia, and 1.4% grade 2-3 dysphagia (Data Supplement, Table S3). Ninety-six percent of patients treated with 70 Gy experienced acute dysphagia versus 57% in the 30-Gy cohort (P < .001; Table 2). Acute toxicities were significantly reduced favoring 30 Gy versus 70 Gy (Table 2). Greater than ninety percent of the reported radiation-related late toxicities were grade 1 (Data Supplement, Table S3). Late toxicity in the 70-Gy cohort in this study also compared favorably with other contemporary series treating with 70 Gy, likely because of a significantly reduced subclinical dose of 30 Gy from historical practice of treating with 50-63 Gy (Fig 1C).

PROs and Dysphagia

PROs for swallowing were assessed with MDADI,[29] with a mean baseline global score of 87.47 (95% CI, 84.12 to 90.82) to 92.28 (95% CI, 89.58 to 94.99) at 4 months and 94.52 (95% CI, 91.99 to 97.04) at 1 year after chemoradiation (Data Supplement, Fig S2 and Tables S4-S8). These results were consistent with alternative instruments for PRO assessment (EORTC Questionnaire; Data Supplement, Table S9).[30] The results from PRO assessments were concordant with objective assessments of dysphagia using modified barium swallow testing, in which none had moderate dysphagia at 1 year after chemoradiation (Fig 3). The patient-reported COST FACIT financial toxicity instrument[31] did not identify any patient with composite scores lower than baseline, during or after treatment. This suggests that financial distress was likely higher before treatment and gradually decreased after treatment completion (Data Supplement, Fig S3).

Exploratory Biomarkers

MRI scans were obtained in a subset of consented patients (n = 95) to evaluate tumor volume and ADC, with the latter as a proxy for the burden of total tumor cells obtained from DW-MRI. Neither pretreatment tumor volume nor mean ADCs, nor a change in these metrics 2 weeks intratreatment accurately identified the 128 patients who were eligible for 30 Gy on the basis of FMISO PET (Data Supplement, Figs S4 and S5). Moreover, ctDNA was persistently detectable in 64% of patients 2 weeks into chemoradiotherapy, suggesting that this marker could not accurately select all 128 patients on the basis of FMISO PET eligible for 30 Gy de-escalation (Data Supplement, Fig S6). The high levels of persistent ctDNA early during chemoradiation are consistent with those of other groups.[32,33]

DISCUSSION

The ability to direct radiotherapy dose on the basis of biologic features in clinical practice is absent for most cancers.[34-36]

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	30 Gy (n = 128), No. (%)	70 Gy (n = 24), No. (%)	Total (n = 152), No. (%)
Sex			
Male	115 (89.8)	22 (91.7)	137 (90.1)
Female	13 (10.2)	2 (8.3)	15 (9.9)
Age, years			
≤49	15 (11.7)	4 (16.7)	19 (12.5)
50-59	55 (43.0)	12 (50.0)	67 (44.1)
60-69	49 (38.3)	8 (33.3)	57 (37.5)
≥70	9 (7.0)	0 (0)	9 (5.9)
Race			
White	117 (91.4)	23 (95.8)	140 (92.1)
Asian/Far East/Indian subcontinent	2 (1.5)	0 (0)	2 (1.3)
Black or African American	1 (0.8)	0 (0)	1 (0.7)
Unknown or not reported	8 (6.3)	1 (4.2)	9 (5.9)
Smoking			
Never	74 (57.8)	6 (25.0)	80 (52.6)
≤10 pack-years	28 (21.9)	9 (37.5)	37 (24.3)
>10 pack-years	26 (20.3)	9 (37.5)	35 (23.0)
ECOG performance status			
0	101 (78.9)	20 (83.3)	121 (79.6)
1	27 (21.1)	4 (16.7)	31 (20.4)
Primary site			
Tonsil	72 (56.3)	12 (50.0)	84 (55.2)
BOT	36 (28.1)	5 (20.8)	41 (27.0)
Unknown	20 (15.6)	7 (29.2)	27 (17.8)
HPV RNA-ISH			
Positive	123 (96.1)	23 (95.8)	146 (96.1)
Unknown	5 (3.9)	1 (4.2)	6 (3.9)
p16 status			
Positive	128 (100)	24 (100)	152 (100)
Negative	0 (0)	0 (0)	0 (0)
T class			
0	20 (15.6)	7 (29.2)	27 (17.8)
1	64 (50.0)	10 (41.7)	74 (48.6)
2	44 (34.4)	7 (29.2)	51 (33.6)
N class			
1	14 (10.9)	3 (12.5)	17 (11.2)
2a	11 (8.5)	3 (12.5)	14 (9.2)
2b	76 (59.4)	16 (66.7)	92 (60.5)
2c	27 (21.1)	2 (8.3)	29 (19.1)
Grouping			
III	14 (10.9)	3 (12.5)	17 (11.2)
IVA	114 (89.1)	21 (87.5)	135 (88.8)
RTOG risk group			
Low	107 (83.6)	19 (79.2)	126 (82.9)
Intermediate	21 (16.4)	5 (20.8)	26 (17.1)
Chemotherapy regimen			
Cisplatin	110 (85.9)	22 (91.7)	132 (86.8)
Carbo/5FU	18 (14.1)	2 (8.3)	20 (13.2)

(continued on following page)

TABLE 1. Baseline Demographic and Clinical Characteristics (continued)

Characteristic	30 Gy (n = 128), No. (%)	70 Gy (n = 24), No. (%)	Total (n = 152), No. (%)
Margin status			
Negative	17 (15.7)	4 (23.5)	21 (16.8)
Close (<2 mm)	57 (52.8)	7 (41.2)	64 (51.2)
Positive (on ink)	34 (31.4)	6 (35.3)	40 (32.0)

Abbreviations: 5FU, fluorouracil; BOT, base of tongue; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; ISH, in situ hybridization; RTOG, Radiation Therapy Oncology Group.

Studies attempting to de-escalate therapy for HPV-related oropharyngeal carcinoma have led to inferior oncologic outcomes[3,4,6,12] without significant toxicity reduction.[7-9] Notably, toxicity in aggregate is also not dramatically reduced in surgical de-escalation studies where patients still received a high radiation dose of 50 Gy-60 Gy (60% of the patients) or chemoradiotherapy to 66 Gy with cisplatin (30% of the patients).[8] Without selection, modest dose de-escalation to 60 Gy leads to inferior oncologic outcomes.[12] Here, we used FMISO PET to personalize radiotherapy dose to 30 Gy[26] and we report a 2-year LRC of 95% with a favorable toxicity profile.[18,21-23,25,37,38] It should be noted that 12 of 128 (9%) patients who received 30 Gy required neck dissections versus 2%-8% in other series.[3,4,6,7,9]

PET imaging with various radiotracers has been used for risk stratification and treatment modification in a variety of diseases.[39,40] We used FMISO PET response to direct radiation

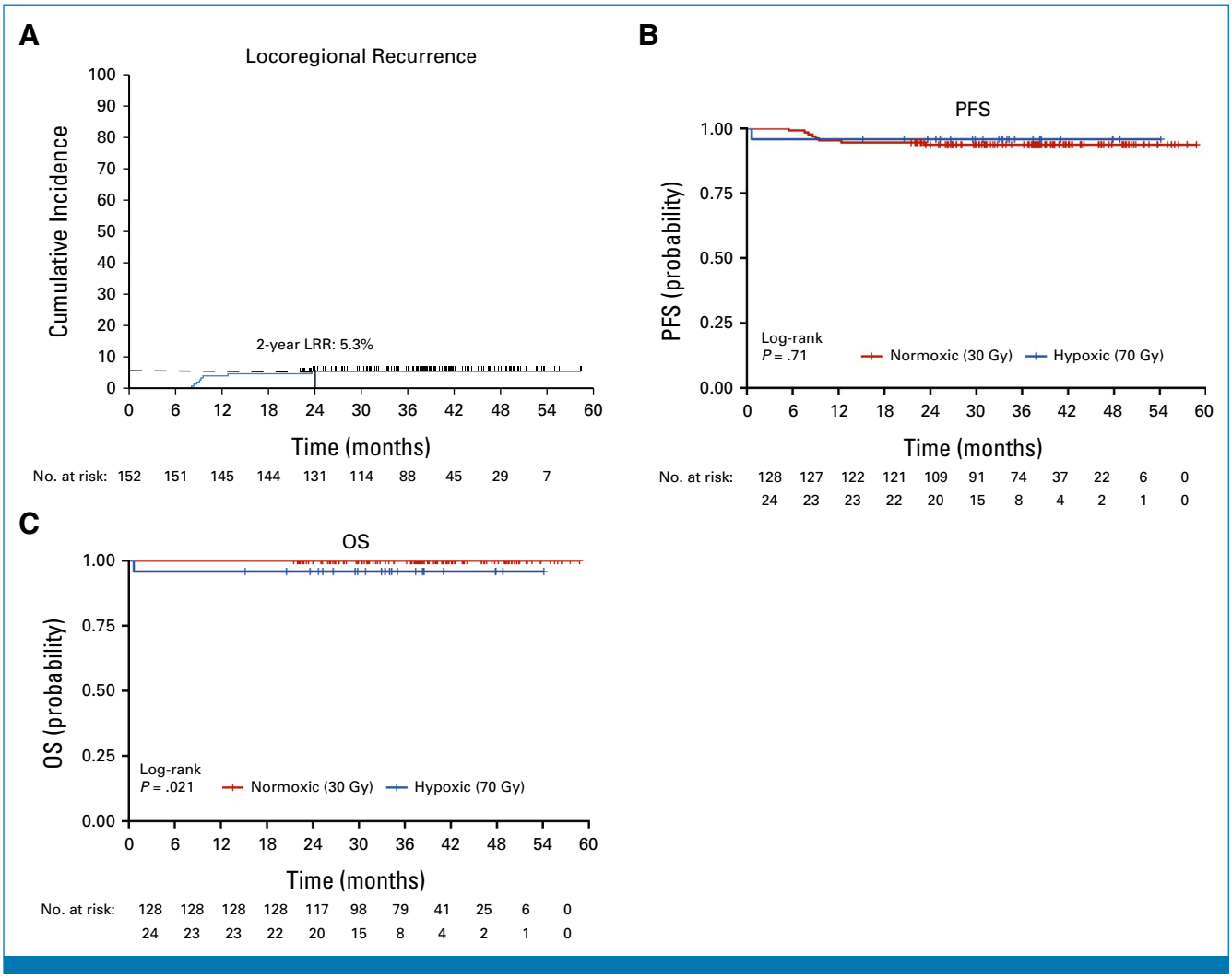

FIG 2. Oncologic outcomes. (A) Cumulative incidence of LRR for the entire cohort using competing risk analysis. (B) PFS by treatment group. (C) OS by treatment group. LRR, locoregional recurrence; OS, overall survival; PFS, progression-free survival.

TABLE 2. Most Common Investigator-Reported Adverse Events for the 30-Gy and 70-Gy Cohort

	30 Gy, %		70 Gy, %		
Acute Toxicity	Any	Grade 3-4	Any	Grade 3-4	*P*
RT-related					
Dermatitis	47.6	0.0	95.8	4.2	<.001
Dry mouth	89.1	0.0	100.0	0.0	.16
Dysphagia	57.0	0.7	95.8	8.3	<.001
Oral mucositis	78.9	0.0	95.8	4.2	<.001
Dysgeusia	93.8	0.0	100.0	0.0	<.001
Hypothyroidism	6.3	0.0	12.5	0.0	.38
Chemotherapy-related					
Neutropenia	57.0	29.7	79.2	45.8	.15
Anemia	85.9	0.7	95.8	4.2	.003
Thrombocytopenia	73.4	0.0	79.1	0.0	.01
Nausea	44.5	0.7	66.7	4.2	.08
Vomiting	9.4	1.5	12.5	0.0	.67
Neuropathy	3.9	0.0	8.3	0.0	.31
Acute kidney injury	42.9	0.7	62.5	4.2	.07
Hearing	8.6	0.0	8.3	0.0	1

	30 Gy, %		70 Gy, %		
Late Toxicity	Any	Grade 3-4	Any	Grade 3-4	*P*
RT-related					
Dermatitis	0.0	0.0	0.0	0.0	1
Dry mouth	81.3	0.0	95.5	0.0	.25
Dysphagia	11.7	0.0	18.1	4.5	.22
Oral mucositis	3.1	0.0	0.0	0.0	1
Dysgeusia	73.4	0.0	86.4	0.0	.23
Hypothyroidism	12.5	0.0	31.8	0.0	.05
Chemotherapy-related					
Neutropenia	3.9	0.0	0.0	0.0	1
Anemia	31.3	0.7	40.9	0.0	.49
Thrombocytopenia	16.4	0.0	36.6	0.0	.03
Nausea	0.7	0.0	4.5	0.0	.28
Vomiting	0.0	0.0	0.0	0.0	1
Neuropathy	6.3	0.0	9.1	0.0	.65
Kidney injury	18.0	0.0	36.3	0.0	.09
Hearing	12.5	0.0	9.1	0.0	1

Abbreviation: RT, radiation therapy.

dose because multiple groups have shown that a positive FMISO scan is a poor prognostic biomarker of radiotherapy cancer outcomes including HPV-related oropharyngeal carcinoma.[18,21-23,25,37,38] Despite its lower TBR versus other PET imaging agents, our hybrid qualitative/quantitative method of interpreting FMISO PET has excellent interobserver agreement in identifying hypoxia ($\kappa = 0.859$; 95% CI, 0.761 to 0.944) between five nuclear medicine physicians with various levels of experience[28] (Appendix Table A1). This interpretation method is similar to other established PET criteria, that is, Lugano criteria in lymphoma[37] and PROMISE PSMA PET method for prostate cancer.[38] The consistency of FMISO reads, combined with its commercial availability and the ability to produce it with a cyclotron, facilitates its adoption across institutions. However, we acknowledge that using FMISO PET in a multicenter randomized trial to tailor radiotherapy dose presents challenges for implementation into clinical practice. We have tested the feasibility of using FMISO PET to de-escalate HPV-related oropharyngeal cancers enrolling patients from other centers (n = 10) in a subsequent study that completed accrual.

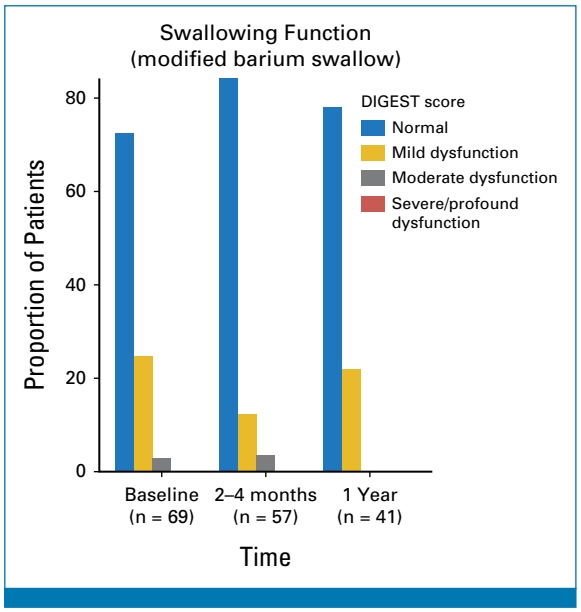

FIG 3. Toxicity and dysphagia-related outcomes. Modified barium swallow objective assessments using DIGEST score (0 is within normal limits, and 4 denotes profound dysphagia) for the 30-Gy cohort.

Patients who received 30 Gy had significantly lower rates of acute toxicity versus 70 Gy. None of the 30 Gy patients had moderate dysphagia 1 year after chemoradiation versus the historical rates of 30% at 3-6 months and 15% 2 years after chemoradiation.[41,42] Overall, toxicity with our de-escalated approach compares favorably with standard chemoradiotherapy observed on contemporary randomized trials.[3,4] Although our patients had slightly less advanced disease than those in RTOG 10-16 and DeEscalate, similar toxicities were observed in the 60-Gy arm of NRG HN-002 as those two studies.[9] Notably, NRG HN-002 trial included patients with less advanced neck disease than ours, suggesting that the toxicity differences are mainly due to changes in radiotherapy dose.

Previous work has illustrated that MRI-derived parameters are predictive of treatment response after 70 Gy of chemoradiation for head and neck cancer[43-46]; however, its role in de-escalation remains an active area of investigation. We were not able to predict hypoxia resolution on the basis of MRI parameters. Further work will be required to elucidate which MR imaging modality or if a multimodal imaging approach may be optimal to identify patients for de-escalation. The attenuated radiation dose also reduced financial toxicity for our patients. Furthermore, using expected Medicare hospital and physician reimbursement as a proxy, we found a 63% decrease in the overall direct cost of health care services among patients who underwent 30 Gy versus 70 Gy.

Limitations of this study are that we have not comprehensively evaluated the performance of FMISO PET as a biomarker for radical de-escalation and that FMISO PET has a limited amount of evidence as a prognostic biomarker for HPV-related oropharyngeal carcinoma.[25] At the time of initiation of this study (2017), chemoradiotherapy to 30 Gy in an unselected population would be considered unethical, rendering a definitive evaluation of the performance of FMISO PET as a biomarker not feasible. Emerging data, however, suggest that biomarker selection is necessary for de-escalation of chemoradiotherapy in HPV-related OPC.[12] Additional limitations are that this is a single-arm study with relatively short follow-up (median slightly >3 years) in a selected subset of HPV-related oropharyngeal carcinomas with primary tumors amenable to surgery and that the toxicities associated with surgical resection of the primary were not accounted for.

In conclusion, to our knowledge, we report the first personalized phase II trial using functional PET imaging as an integral biomarker to markedly de-escalate definitive chemoradiotherapy in head and neck cancer. This approach significantly decreased adverse events, while producing oncologic outcomes comparable with the standard full-dose radiotherapy. Although such results are promising, further evaluation is required before it can be considered for routine use in clinical practice. A phase III trial is currently being planned to compare this precision radiotherapy approach with the current standard of care, building on the tenets of personalized targeted therapy to usher a new paradigm of biomarker-directed therapy for patients with HPV-related oropharyngeal cancer.

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Hypoxia-Directed Treatment of Human Papillomavirus–Related Oropharyngeal Carcinoma

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APPENDIX

TABLE A1. Detailed Patient Characteristics Including Details on FMISO PET Scan

Patient	T Stage	N Stage	Primary Site	Smoking Status	Margin Status	Chemotherapy Regimen	Pretreatment FMISO PET Result	Pretreatment TMR	On-Treatment FMISO PET Result	On-Treatment TMR	Locoregional Recurrence	Any Neck Dissection
1	T2	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.133333333	Negative	0.944444444	No	No
2	T2	N2b	BOT	Never	Positive	Cisplatin	Hypoxic	1.714285714	Negative	0.9375	No	No
3	T1	N1	Tonsil	Never	Close	Cisplatin	Negative	1	NA	NA	No	No
4	T2	N2b	Tonsil	<10 pack-years	Positive	Both	Hypoxic	1.428571429	Hypoxic	1	No	No
5	T1	N2b	BOT	Never	Close	Cisplatin	Hypoxic	1.6	Negative	1.0625	No	No
6	T1	N2b	BOT	Never	Negative	Cisplatin	Negative	1	NA	NA	No	No
7	T1	N2b	BOT	>10 pack-years	Negative	Cisplatin	Hypoxic	1.705882353	Hypoxic	1.05	No	No
8	T2	N2c	BOT	>10 pack-years	Negative	Cisplatin	Hypoxic	1.642857143	Negative	0.761904762	No	No
9	T0	N2b	Unknown	Never	NA—unknown primary	Cisplatin	Hypoxic	1.058823529	Negative	1.133333333	No	No
10	T1	N2b	BOT	Never	Close	Cisplatin	Hypoxic	1.5	Negative	1	No	No
11	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.714285714	Negative	1.0625	No	No
12	T1	N2b	Tonsil	Never	Positive	Cisplatin	Hypoxic	2.230769231	Negative	1	No	No
13	T1	N2b	Tonsil	Never	Positive	Cisplatin	Hypoxic	1.333333333	Negative	1.066666667	No	No
14	T1	N2c	BOT	Never	Negative	Cisplatin	Hypoxic	1.214285714	Negative	1	No	No
15	T1	N2b	BOT	Never	Negative	Carbo/5FU	Hypoxic	1.333333333	Negative	1.058823529	No	No
16	T1	N2b	BOT	<10 pack-years	Close	Cisplatin	Hypoxic	1.333333333	Negative	0.928571429	No	No
17	T1	N2b	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	2	Negative	0.8125	No	No
18	T1	N2b	Tonsil	Never	Positive	Cisplatin	Negative	1.176470588	NA	NA	No	No
19	T2	N2b	Tonsil	Never	Positive	Carbo/5FU	Negative	0.823529412	NA	NA	No	No
20	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	3.090909091	Negative	1.076923077	No	No
21	T2	N2c	Tonsil	<10 pack-years	Positive	Cisplatin	Hypoxic	2.125	Negative	1	No	No
22	T1	N2b	Tonsil	Never	Close	Carbo/5FU	Hypoxic	1.5	Negative	1.066666667	No	No
23	T2	N2c	Tonsil	Never	Positive	Carbo/5FU	Negative	1.214285714	NA	NA	No	No
24	T1	N2c	Tonsil	<10 pack-years	Close	Cisplatin	Hypoxic	2.333333333	Hypoxic	1.615384615	No	No
25	T1	N2c	BOT	<10 pack-years	Positive	Cisplatin	Negative	0.941176471	NA	NA	No	No
26	T2	N2b	BOT	Never	Negative	Cisplatin	Hypoxic	1.625	Negative	1.0625	No	No
27	T1	N2c	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	1.923076923	Hypoxic	1.333333333	No	No
28	T0	N2a	Unknown	>10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.578947368	Hypoxic	1.526315789	No	No
29	T1	N2b	BOT	Never	Negative	Cisplatin	Hypoxic	1.25	Negative	0.882352941	No	No
30	T2	N2c	Tonsil	<10 pack-years	Close	Carbo/5FU	Negative	0.714285714	NA	NA	No	No
31	T2	N2b	BOT	Never	Positive	Cisplatin	Hypoxic	1	Negative	1.066666667	No	No
32	T1	N2b	Tonsil	Never	Close	Cisplatin	Negative	1.071428571	NA	NA	No	No
33	T1	N1	BOT	Never	Negative	Cisplatin	Negative	0.882352941	NA	NA	No	No
34	T1	N1	BOT	Never	Positive	Cisplatin	Negative	0.6875	NA	NA	No	No
35	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.4375	Negative	1	No	No

(continued on following page)

TABLE A1. Detailed Patient Characteristics Including Details on FMISO PET Scan (continued)

Patient	T Stage	N Stage	Primary Site	Smoking Status	Margin Status	Chemotherapy Regimen	Pretreatment FMISO PET Result	Pretreatment TMR	On-Treatment FMISO PET Result	On-Treatment TMR	Locoregional Recurrence	Any Neck Dissection
36	T2	N2c	Tonsil	>10 pack-years	Close	Cisplatin	Negative	0.947368421	NA	NA	No	No
37	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.25	Negative	1	No	No
38	T1	N2b	Tonsil	<10 pack-years	Close	Carbo/5FU	Hypoxic	1.73	Hypoxic	1.733333333	No	No
39	T2	N1	Tonsil	Never	Positive	Cisplatin	Negative	1.230769231	NA	NA	No	No
40	T2	N2b	BOT	>10 pack-years	Positive	Cisplatin	Hypoxic	1.375	Hypoxic	1.3125	No	No
41	T0	N2b	Unknown	Never	NA—unknown primary	Cisplatin	Hypoxic	1.2	Negative	0.941176471	Yes	Yes
42	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.133333333	Negative	0.625	Yes	Yes
43	T1	N2b	BOT	>10 pack-years	Negative	Cisplatin	Hypoxic	2.307692308	Hypoxic	1.769230769	No	No
44	T0	N2b	Unknown	<10 pack-years	NA—unknown primary	Carbo/5FU	Hypoxic	1.266666667	Negative	1	No	No
45	T1	N2c	Tonsil	>10 pack-years	Close	Cisplatin	Negative	0.8	NA	NA	No	No
46	T2	N2b	BOT	<10 pack-years	Positive	Cisplatin	Hypoxic	1.533333333	Hypoxic	1.176470588	No	No
47	T2	N2b	Tonsil	>10 pack-years	Positive	Cisplatin	Negative	1	NA	NA	Yes	Yes
48	T0	N2b	Unknown	>10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.538461538	Negative	0.882352941	No	No
49	T1	N2b	Tonsil	Never	Negative	Cisplatin	Hypoxic	1.642857143	Negative	1	No	No
50	T1	N2c	Tonsil	Never	Positive	Carbo/5FU	Negative	1.076923077	NA	NA	No	No
51	T2	N2c	Tonsil	Never	Positive	Carbo/5FU	Hypoxic	2.857142857	Negative	0.894736842	No	No
52	T2	N1	BOT	10 pack-years	Close	Cisplatin	Hypoxic	1.230769231	Negative	1.083333333	No	No
53	T1	N2b	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	1.3125	Negative	1.333333333	No	No
54	T2	N2b	Tonsil	Never	Positive	Cisplatin	Hypoxic	2.176470588	Negative	0.944444444	No	No
55	T2	N2b	Tonsil	Never	Close	Cisplatin	Negative	0.857142857	NA	NA	No	No
56	T0	N2b	Unknown	<10 pack-years	NA—unknown primary	Carbo/5FU	Hypoxic	2.428571429	Negative	1	No	No
57	T0	N2b	Unknown	>10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.733333333	Negative	1	No	No
58	T1	N2b	Tonsil	Never	Close	Carbo/5FU	Negative	1.2	NA	NA	No	No
59	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	2.076923077	Negative	1.214285714	No	No
60	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.875	Hypoxic	1.357142857	No	No
61	T2	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1	Negative	0.888888889	No	No
62	T0	N2b	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.285714286	Hypoxic	1.230769231	No	No
63	T0	N2b	Unknown	Never	NA—unknown primary	Cisplatin	Negative	1.307692308	NA	NA	No	No
64	T2	N1	Tonsil	Never	Positive	Carbo/5FU	Negative	0.92	NA	NA	No	No
65	T1	N1	Tonsil	Never	Close	Cisplatin	Negative	0.733333333	NA	NA	No	No
66	T1	N2a	Tonsil	Never	Close	Cisplatin	Hypoxic	1	Negative	1	No	No
67	T1	N2b	BOT	Never	Positive	Cisplatin	Negative	1.058823529	NA	NA	No	No
68	T0	N2b	Unknown	Never	NA—unknown primary	Carbo/5FU	Negative	0.8	NA	NA	No	No
69	T1	N2c	BOT	<10 pack-years	Positive	Cisplatin	Negative	1.058823529	NA	NA	No	No
70	T1	N2b	Tonsil	<10 pack-years	Close	Cisplatin	Negative	1.0625	NA	NA	No	No
71	T2	N2b	Tonsil	<10 pack-years	Close	Carbo/5FU	Hypoxic	1.166666667	Negative	0.736842105	Yes	Yes
72	T2	N2b	Tonsil	Never	Positive	Cisplatin	Hypoxic	1.0625	Negative	1.125	No	No

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TABLE A1. Detailed Patient Characteristics Including Details on FMISO PET Scan (continued)

Patient	T Stage	N Stage	Primary Site	Smoking Status	Margin Status	Chemotherapy Regimen	Pretreatment FMISO PET Result	Pretreatment TMR	On-Treatment FMISO PET Result	On-Treatment TMR	Locoregional Recurrence	Any Neck Dissection
73	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	2.071428571	Negative	1.0625	No	No
74	T1	N2c	Tonsil	Never	Negative	Cisplatin	Hypoxic	2.153846154	Negative	1	No	No
75	T1	N2a	Tonsil	>10 pack-years	Positive	Cisplatin	Negative	0.928571429	NA	NA	No	No
76	T1	N2b	BOT	>10 pack-years	Close	Cisplatin	Hypoxic	1.8125	Negative	1	No	No
77	T1	N2b	BOT	>10 pack-years	Positive	Carbo/5FU	Hypoxic	2	Negative	1.105263158	Yes	Yes
78	T0	N2b	Unknown	>10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	2	Hypoxic	1.182352941	No	No
79	T1	N2c	Tonsil	Never	Close	Cisplatin	Negative	0.823529412	NA	NA	No	No
80	T2	N1	BOT	Never	Positive	Cisplatin	Hypoxic	1.125	Negative	1.0625	No	No
81	T0	N2b	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.684210526	Hypoxic	1.529411765	No	No
82	T2	N2b	Tonsil	Never	Close	Cisplatin	Negative	1	NA	NA	No	No
83	T0	N2b	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Negative	1	NA	NA	No	No
84	T1	N2c	Tonsil	Never	Close	Cisplatin	Hypoxic	1.928571429	Negative	0.941176471	No	No
85	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	2.357142857	Negative	1	No	No
86	T0	N2a	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	2	Negative	1	No	No
87	T1	N2a	Tonsil	<10 pack-years	Positive	Cisplatin	Hypoxic	1.357142857	Negative	1.058823529	No	No
88	T2	N2b	BOT	<10 pack-years	Close	Carbo/5FU	Negative	0.94	NA	NA	No	No
89	T1	N1	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	1.5	Negative	1	No	No
90	T2	N2b	Tonsil	10 pack-years	Positive	Cisplatin	Hypoxic	1.55	Hypoxic	0.94	No	No
91	T0	N1	Unknown	Never	NA—unknown primary	Cisplatin	Hypoxic	0.821428571	Negative	0.842105263	No	No
92	T1	N2a	BOT	Never	Close	Cisplatin	Hypoxic	1.6	Negative	0.947368421	No	Yes
93	T0	N2b	Unknown	Never	NA—unknown primary	Cisplatin	Hypoxic	2.357142857	Hypoxic	1.294117647	No	No
94	T0	N2b	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.625	Negative	1	No	No
95	T0	N2b	Unknown	>10 pack-years	NA—unknown primary	Cisplatin	Negative	0.94	NA	NA	No	No
96	T0	N2c	Unknown	Never	NA—unknown primary	Cisplatin	Negative	1.0625	NA	NA	No	No
97	T1	N2b	Tonsil	<10 pack-years	Close	Cisplatin	Negative	0.9375	NA	NA	No	No
98	T1	N2a	Tonsil	Never	Close	Cisplatin	Hypoxic	1.8	Negative	1	No	No
99	T0	N2a	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.188	Negative	1	No	No
100	T0	N2b	Unknown	Never	NA—unknown primary	Cisplatin	Negative	0.833333333	NA	NA	No	No
101	T2	N2b	Tonsil	>10 pack-years	Negative	Cisplatin	Hypoxic	1.894736842	Negative	1.052631579	No	No
102	T1	N2c	BOT	<10 pack-years	Negative	Cisplatin	Hypoxic	2.692307692	Negative	1	Yes	Yes
103	T2	N2b	Tonsil	<10 pack-years	Close	Cisplatin	Hypoxic	1.4	Negative	1	No	No
104	T2	N2b	Tonsil	>10 pack-years	Close	Cisplatin	Negative	1	NA	NA	No	No
105	T1	N1	BOT	>10 pack-years	Negative	Cisplatin	Negative	1	NA	NA	No	No
106	T1	N2b	BOT	<10 pack-years	Close	Carbo/5FU	Hypoxic	1.25	Negative	0.888888889	No	No
107	T2	N2b	BOT	>10 pack-years	Positive	Cisplatin	Hypoxic	1.666666667	Negative	0.9375	No	No
108	T1	N1	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	1.8	Hypoxic	1.538461538	No	No
109	T0	N1	Unknown	>10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.6	Hypoxic	1.357142857	No	No

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TABLE A1. Detailed Patient Characteristics Including Details on FMISO PET Scan (continued)

Patient	T Stage	N Stage	Primary Site	Smoking Status	Margin Status	Chemotherapy Regimen	Pretreatment FMISO PET Result	Pretreatment TMR	On-Treatment FMISO PET Result	On-Treatment TMR	Locoregional Recurrence	Any Neck Dissection
110	T2	N2b	Tonsil	>10 pack-years	Positive	Cisplatin	Hypoxic	2.428571429	Negative	1	No	No
111	T1	N2c	Tonsil	Never	Positive	Cisplatin	Hypoxic	1.357142857	Negative	0.823529412	No	No
112	T1	N1	BOT	Never	Close	Cisplatin	Hypoxic	1.307692308	Negative	0.769230769	No	No
113	T2	N2b	BOT	>10 pack-years	Positive	Both	Hypoxic	1.866666667	Negative	1	No	No
114	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.928571429	Hypoxic	2	No	No
115	T2	N1	Tonsil	>10 pack-years	Positive	Cisplatin	Negative	0.933333333	NA	NA	No	No
116	T2	N2b	Tonsil	<10 pack-years	Negative	Cisplatin	Hypoxic	1.2	Negative	1	No	No
117	T1	N2b	BOT	>10 pack-years	Close	Cisplatin	Hypoxic	1.727272727	Negative	1.176470588	No	No
118	T1	N2c	Tonsil	>10 pack-years	Close	Cisplatin	Negative	0.75	NA	NA	No	No
119	T2	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	2.714285714	Negative	1	No	No
120	T2	N2b	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	1.285714286	Negative	1.066666667	No	No
121	T2	N2b	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	1.470588235	Negative	1.105263158	No	No
122	T1	N2b	Tonsil	<10 pack-years	Close	Cisplatin	Negative	0.888888889	NA	NA	No	Yes
123	T2	N2b	Tonsil	>10 pack-years	Close	Cisplatin	Hypoxic	1.470588235	Negative	1.058823529	No	No
124	T2	N1	Tonsil	Never	Positive	Cisplatin	Hypoxic	1.333333333	Hypoxic	1.133333333	No	No
125	T2	N2c	BOT	Never	Positive	Both	Hypoxic	2	Negative	0.941176471	Yes	Yes
126	T2	N2a	BOT	>10 pack-years	Positive	Cisplatin	Hypoxic	2.214285714	Negative	1	No	No
127	T2	N2c	Tonsil	Never	Positive	Cisplatin	Hypoxic	1.789473684	Negative	1.055555556	No	No
128	T0	N2b	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.2	Negative	1	No	No
129	T1	N2a	Tonsil	Never	Negative	Cisplatin	Hypoxic	1.45	Hypoxic	1.777777778	No	No
130	T1	N2a	BOT	Never	Close	Cisplatin	Hypoxic	2.066666667	Negative	0.875	No	No
131	T2	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1	Negative	0.739130435	No	No
132	T2	N2b	BOT	Never	Close	Carbo/5FU	Negative	1.142857143	NA	NA	No	No
133	T2	N2b	Tonsil	Never	Positive	Carbo/5FU	Hypoxic	1.733333333	Hypoxic	1.307692308	No	No
134	T1	N2b	Tonsil	Never	Close	Cisplatin	Hypoxic	1.625	Negative	1.307692308	Yes	Yes
135	T0	N2a	Unknown	>10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	3.428571429	Hypoxic	1.9375	No	No
136	T2	N2b	Tonsil	<10 pack-years	Close	Cisplatin	Hypoxic	1.647058824	Hypoxic	1.176470588	No	No
137	T1	N2c	Tonsil	<10 pack-years	Positive	Cisplatin	Hypoxic	2.944444444	Negative	0.9	No	No
138	T2	N2b	Tonsil	Never	Close	Cisplatin	Negative	1.055555556	NA	NA	No	No
139	T1	N2b	Tonsil	Never	Positive	Cisplatin	Negative	0.947368421	NA	NA	No	No
140	T2	N2c	Tonsil	Never	Close	Cisplatin	Hypoxic	3.142857143	Negative	1	No	No
141	T1	N2b	Tonsil	<10 pack-years	Close	Carbo/5FU	Hypoxic	1.285714286	Negative	0.933333333	No	No
142	T1	N1	Tonsil	10 pack-years	Negative	Cisplatin	Hypoxic	1.428571429	Negative	1.125	No	No
143	T1	N2b	Tonsil	<10 pack-years	Close	Cisplatin	Hypoxic	1.692307692	Negative	1.181818182	No	No
144	T0	N2c	Unknown	Never	NA—unknown primary	Cisplatin	Hypoxic	1.117647059	Negative	1.066666667	No	Yes
145	T2	N2b	Tonsil	Never	Negative	Cisplatin	Hypoxic	1.066666667	Negative	0.875	No	No
146	T1	N2a	BOT	Never	Close	Cisplatin	Hypoxic	1.5	Negative	1	No	No

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TABLE A1. Detailed Patient Characteristics Including Details on FMISO PET Scan (continued)

Patient	T Stage	N Stage	Primary Site	Smoking Status	Margin Status	Chemotherapy Regimen	Pretreatment FMISO PET Result	Pretreatment TMR	On-Treatment FMISO PET Result	On-Treatment TMR	Locoregional Recurrence	Any Neck Dissection
147	T0	N2c	Unknown	Never	NA—unknown primary	Cisplatin	Hypoxic	1.8	Negative	1	No	No
148	T1	N2c	BOT	Never	Negative	Cisplatin	Hypoxic	1.3125	Negative	1	No	Yes
149	T1	N2a	Tonsil	Never	Positive	Cisplatin	Negative	1.105263158	NA	NA	No	No
150	T1	N2b	BOT	<10 pack-years	Negative	Cisplatin	Hypoxic	1.866666667	Hypoxic	1.214285714	No	No
151	T2	N2c	BOT	Never	Negative	Cisplatin	Hypoxic	1.1875	Negative	1.142857143	No	No
152	T0	N2c	Unknown	<10 pack-years	NA—unknown primary	Cisplatin	Hypoxic	1.133333333	Negative	0.933333333	No	No

Abbreviations: 5FU, fluorouracil; BOT, base of tongue; FMISO PET, 18F-fluoromisonidazole positron emission tomography; N, nodal; NA, not available; T, tumor; TMR, tumor to muscle ratio.