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ABSTRACT

BACKGROUND AND PURPOSE: FDG PET/CT has a high negative predictive value in patients with head and neck squamous cell carcinoma who responds completely to non-operative therapy. However, the treatment failure rate in patients with a partial but incomplete response is unclear. Our aim was to investigate the negative predictive value of the first posttreatment FDG-PET/CT in patients with head and neck squamous cell carcinoma with incomplete response interpreted as Neck Imaging Reporting and Data System (NI-RADS) category 2.

MATERIALS AND METHODS: We retrospectively identified patients with head and neck squamous cell carcinoma treated with chemoradiation or radiation therapy with curative intent in our institution between 2008 and 2016. We included patients whose first posttreatment FDG-PET/CT was interpreted as showing marked improvement of disease but who had a mild residual mass or FDG avidity in either the primary tumor bed or lymph nodes (NI-RADS 2). The negative predictive value of FDG-PET/CT was calculated, including the 95% CI, using the Newcombe method. Two-year disease-free survival was the reference standard.

RESULTS: Seventeen of 110 patients (15%) experienced locoregional treatment failure within 2 years of completing treatment, yielding a negative predictive value of 85% (95% CI, 77%–90%). The most common location of tumor recurrence was the cervical lymph nodes (59%). The median time interval between completion of therapy and treatment failure was 10 months (range, 5–24 months).

CONCLUSIONS: In patients with an incomplete response after treatment of head and neck squamous cell carcinoma, the negative predictive value of the first posttreatment FDG-PET/CT was 85%, which is lower than the 91% negative predictive value of FDG-PET/CT in patients with an initial complete response. Patients with an incomplete response (NI-RADS 2) should undergo more frequent clinical and imaging surveillance than patients with an initial complete response (NI-RADS 1).

ABBREVIATIONS: AJCC = American Joint Committee on Cancer; HNSCC = head and neck squamous cell carcinoma; IR = incomplete response; NI-RADS = Neck Imaging Reporting and Data System; NPV = negative predictive value; TF = treatment failure

PET/CT is critical to the management of patients with head and neck squamous cell carcinoma (HNSCC), given its high accuracy in pretreatment staging and the detection of persistent and recurrent disease after therapy compared with CT or MR imaging, allowing salvage treatment to be initiated in a timely manner.[1-12] The high negative predictive value (NPV) of posttreatment PET/CT in patients with a complete response has been established.[10] It was demonstrated in a prospective, randomized controlled trial that concluded that planned neck dissection can be deferred in patients with HNSCC with a complete response on initial posttreatment PET/CT following definitive chemoradiation therapy.[11,13] However, the treatment failure (TF) rate in patients who have a partial, incomplete response (IR) on the initial posttreatment PET/CT remains controversial, and management of an initial IR is inconsistent.[14,15]

The American College of Radiology has recently published the Neck Imaging Reporting and Data System (NI-RADS), a standardized radiologic reporting system for head and neck cancer imaging to facilitate communication between radiologists and referring physicians and to determine the appropriate next management steps for an individual patient.[16] This reporting system also assists in sharing data among institutions, which may facilitate the advancement of head and neck cancer research. In NI-RADS, the results of posttreat-

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ment imaging surveillance are classified into 4 numeric categories based on imaging suspicion for residual or recurrent tumors (category 1, no evidence of recurrence; category 2, low suspicion; category 3, high suspicion; category 4, definitive disease recurrence).[16-18]

The purpose of this study was to investigate the NPV of the first posttreatment FDG-PET/CT in patients with HNSCC with an IR interpreted as NI-RADS category 2.

MATERIALS AND METHODS

Study Design and Patient Selection

We conducted a retrospective study that was approved by our institutional review board (PRO08120419) and was in compliance with the Health Insurance Portability and Accountability Act. Medical records from our institutional Head and Neck Oncologic Data Repository were reviewed to include patients with histologically confirmed HNSCC treated with primary definitive chemoradiation therapy or radiation therapy at our institution between 2008 and 2016 with available contrast-enhanced staging imaging and at least 24 months of clinical and radiographic follow-up at our institution after the conclusion of treatment. Patients who had non-squamous cell malignancies or a history of previously treated head and neck cancer were excluded. Pretreatment tumor staging of all patients was performed using the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*, 7th edition.[19] We selected patients whose first posttreatment PET/CT was performed 2–3 months after the completion of treatment and was interpreted as showing marked improvement in size and/or FDG avidity of a locoregional tumor, but with persistent mild FDG avidity relative to background and/or small residual soft tissue at either the treated primary tumor site or regional metastatic lymph nodes. These PET/CT findings were categorized as NI-RADS 2 (low suspicion for residual viable tumor). These patients can be divided into 3 major groups: 1) patients who had a partial IR at the primary tumor beds, with complete response at regional nodal sites (P2N1); 2) patients who had a complete response at primary tumor beds, but partial IR at regional nodal sites (P1N2); and 3) patients who had a partial IR at both primary tumor beds and regional nodal sites (P2N2).

These patients were followed clinically and radiologically for 2 years after the conclusion of treatment to determine TF rates; TF was defined as the persistence of viable residual tumor or locoregional tumor recurrence after a disease-free interval. TF was confirmed by means of histopathology or unequivocal evidence of disease progression on subsequent imaging and clinical evaluation.

PET/CT Parameters

PET/CTs were performed on several PET/CT scanners (Discovery, GE Healthcare, Milwaukee, Wisconsin; and Biograph mCT, Siemens, Erlangen, Germany), ranging from 2 to 64 input channels. Except for water, patients fasted for at least 4–6 hours before the PET/CT scan and were instructed to avoid strenuous exercise before the test. Serum glucose levels were obtained, and imaging was deferred if glucose levels were >200 mg/dL. Each patient received 10–20 mCi of [^{18}F] FDG dosed by body weight, after which the patient remained seated or recumbent in a relaxed environment during the 50-minute radiotracer uptake phase. Axial PET and diagnostic contrast-enhanced CT images were obtained from the calvarial vertex through the upper thighs after urinary voiding. Emission images were obtained at 50–60 minutes after radiopharmaceutical injection. Diagnostic CT images were obtained 45 seconds after administration of 125 mL of intravenous contrast (iopidamol 370 mg I/mL, Isovue-370; Bracco, Princeton, New Jersey). CT parameters included the following: 120–30 kV-(peak); variable milliampere (AutomA; GE Healthcare); pitch, 1.5–2; and collimation, 3.75-mm. The images of the head and neck were reconstructed in 2.5-mm slice thicknesses with a small FOV, whereas the images of the thorax, abdomen, and pelvis were reconstructed in 3.75-mm slice thicknesses with a full-body FOV.

Clinical Assessment, Treatment, and Surveillance Protocol

All patients had staging contrast-enhanced imaging using PET/CT, neck CT, or MR imaging. Patient treatment protocols, including radiation dose and chemotherapy regimen, were determined by the standard practice guidelines of the multidisciplinary head and neck oncology team at our institution. After completion of treatment, patients had clinical surveillance by means of physical examination and endoscopy every 6–8 weeks for the first year per our institutional protocol. The first PET/CT scan was performed approximately 8 weeks after the last course of chemoradiation therapy or radiation therapy, and subsequent PET/CT scans were then performed at 5, 8, and 14 months after therapy.[20] If patients had clinical signs or symptoms suspicious for TF, PET/CT and histologic confirmation were pursued outside the usual imaging surveillance regimen.

Image Interpretation

All PET/CT scans were interpreted in routine clinical workflow by board-certified neuroradiologists with dedicated experience in head and neck radiology. Postprocessing fusion software (Mirada; Mirada Medical, Denver, Colorado) was used to assist in interpretation. The images were interpreted qualitatively, without specific standard uptake value thresholds. Patients were considered appropriate for inclusion in this study if their first surveillance scan showed a marked decrease in the size and FDG avidity of the documented primary tumor and metastatic lymph nodes with only mild residual soft-tissue abnormality and/or FDG uptake at either the primary tumor or regional nodes.

Statistical Methods

The primary outcome measure was 2-year disease-free survival. A 95% confidence interval for the negative predictive value for the first surveillance PET/CT was calculated using the Newcombe method.[21] Disease-free survival was visualized with Kaplan-Meier survival curves. Statistical analyses were performed with SAS Version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

We performed a first posttreatment PET/CT on 2077 patients in our institution between 2008 and 2016. Of these, 464 patients (22%) were classified as having a NI-RADS 2 response. One hundred ten patients met the inclusion criteria, with a mean age of 59

Patient characteristics ($N = 110$)

Characteristics	
Sex	
Male	85 (77%)
Female	25 (23%)
Age (range) (mean) (median) (yr)	30–87, 59, 58
Primary tumor location	
Oropharynx	51 (46%)
Oral cavity	19 (17%)
Larynx	19 (17%)
Hypopharynx	6 (6%)
Nasopharynx	6 (6%)
Unknown primary	5 (5%)
Paranasal sinuses/nasal cavity	4 (3%)
HPV status (oropharynx) ($n = 51$)	
Positive	35 (69%)
Negative	8 (15.5%)
Unknown	8 (15.5%)
Tumor stage (*AJCC Cancer Staging Manual*, 7th ed)	
T-stage	
T0	5 (5%)
T1	22 (20%)
T2	30 (27%)
T3	25 (23%)
T4	28 (25%)
N-stage	
N0	28 (25%)
N1	17 (15%)
N2	61 (57%)
N3	4 (3%)
M-stage	
M0	107 (97%)
M1	3 (3%)
MX	0 (0%)
TNM stage	
I	1 (1%)
II	9 (8%)
III	22 (20%)
IV	78 (71%)
Interval between the first posttreatment PET/CT and completion of chemoradiation (range) (mean) (median) (wk)	3–46, 11, 9
Duration of follow-up (range) (mean) (median) (yr)	1.3–9.7, 4.9, 4.4
Total patients with residual or recurrent disease within 2 yr after completion of primary chemoradiation therapy[a]	17/110 (15%)

Note:—HPV indicates human papillomavirus; TNM, Tumor, Node, Metastasis.
[a] NPV = 85% (95% CI, 77%–90%).

years. Most patients were men ($n = 85$, 77%) with an oropharyngeal primary tumor site ($n = 51$, 46%) and stage IV disease ($n = 78$, 71%). Thirty-five of 51 patients with an oropharyngeal tumor were positive for human papillomavirus (69%). Patient demographics; Tumor, Node, Metastasis staging; treatment; and follow-up information are summarized in the Table.

Seventeen of the 110 patients (15%) experienced locoregional TF within 2 years after treatment completion, yielding an NPV of 85% (95% confidence interval, 77%–90%). Histopathologic confirmation was obtained in 13 patients; 4 patients had no tissue confirmation but had unequivocal clinical and imaging evidence of TF. The characteristics of patients with TF are summarized in the On-line Table. The most common location of locoregional recurrence was the cervical lymph nodes (65%; 11/17). Fifty-three percent (9/17) of patients with TF had oropharyngeal primaries, most of which were positive (56%; 5/9) for human papillomavirus. The median time interval between completion of therapy and locoregional TF was 10 months (range, 5–24 months). The patients with residual FDG avidity had a TF rate like that in the patients who had no residual FDG avidity (16% [13/82] versus 14% [4/28]).

There was no difference in predicting TF between NI-RADS 2 for the nodal site versus NI-RADS 2 for the primary tumor bed (87% versus 86%). Of the 110 patients, 51 patients were scored as having NI-RADS 2 due to IR of metastatic nodal disease (P1N2 and P2N2), and 7 of these patients had TF, yielding an NPV of 86%. Seventy-five patients were scored as having NI-RADS 2 based on positive findings at the primary tumor sites (P2N1 and P2N2), and 10 of these patients developed TF, yielding an NPV of 87%.

Representative PET/CT images of a patient with TF following a posttreatment examination scored as NI-RADS 2 are shown in Fig 1.

DISCUSSION

The NI-RADS classification system for surveillance imaging in HNSCC is used to convey the degree of radiologic certainty regarding the presence of recurrent or residual disease in treated patients.[16-18] Previous work has demonstrated that patients classified in the NI-RADS category 1 on their first surveillance PET/CT have an NPV of 91%.[10] The results from the current study indicate that the NPV in patients with NI-RADS category 2 is lower at 85%. Due to the higher incidence of TF, patients with an IR should undergo more frequent clinical and imaging surveillance than patients with a complete response. For example, at our institution, patients who are categorized as NI-RADS 1 undergo their next imaging surveillance after 6 months, whereas patients categorized as NI-RADS 2 undergo imaging at 3 months. Figure 3[16] demonstrates a scheme for PET/CT surveillance at our institution. This recommendation is applied to patients primarily treated nonoperatively with definitive chemoradiation or radiation therapy.

The literature regarding the TF rates in patients with HNSCC with an initial IR is limited. There are no established treatment or surveillance protocols for these patients. The most recent National Comprehensive Cancer Network guidelines of 2018[22] recommend either observation, fine needle aspiration, or planned neck dissection if the initial 12-week posttreatment PET/CT shows an equivocal response of nodal disease (ie, size of lymph node <1 cm with abnormal FDG uptake which is suspicious for disease or size of the lymph node of >1 cm with no FDG uptake).

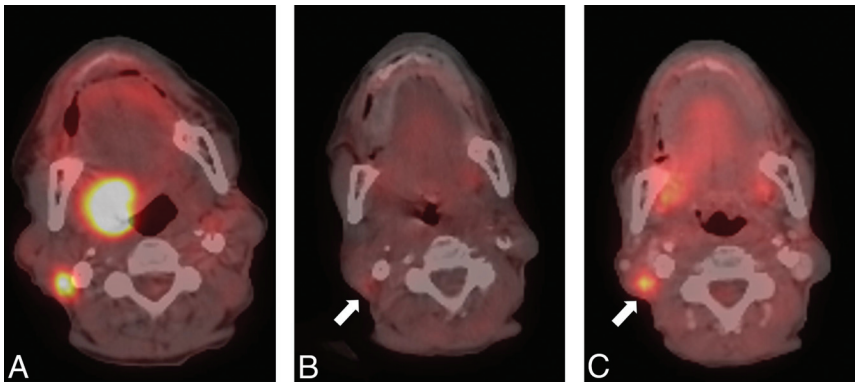

FIG 1. Patient 8. A 69-year-old woman with advanced oropharyngeal squamous cell carcinoma. *A*, Pretreatment PET/CT shows a large FDG-avid right faucial tonsil and lateral oropharyngeal wall tumor with an FDG-avid right level II nodal metastasis. *B*, At 8 months after completion of therapy, there is complete response of the primary tumor but mild residual FDG uptake in the treated right level II node. *C*, Surveillance PET/CT scan obtained at 16 months after treatment shows increased FDG avidity and size of the right level II node, consistent with regional treatment failure, confirmed by salvage neck dissection. There is no disease recurrence at the primary tumor site.

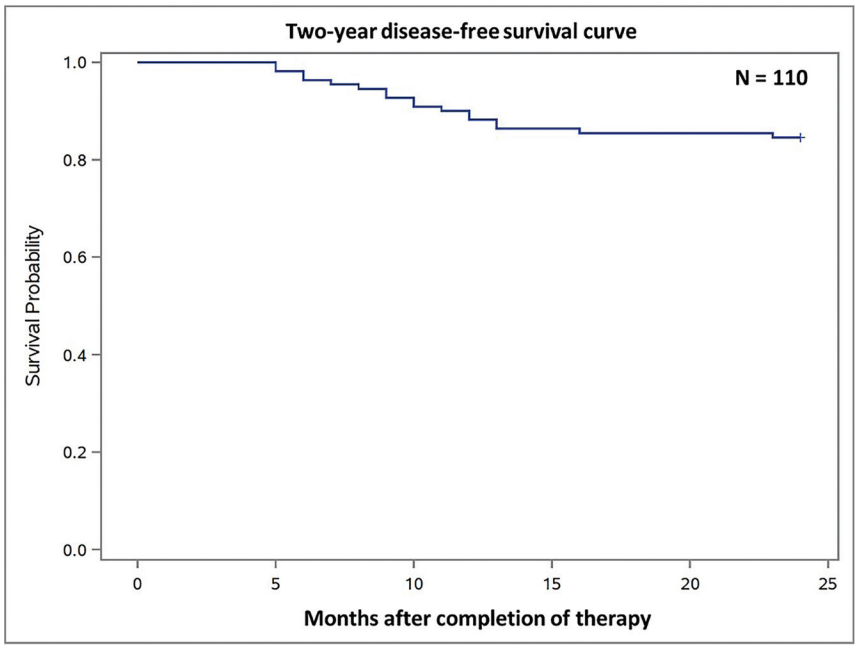

FIG 2. Two-year disease-free survival curve of patients with HNSCC with an incomplete response on the first posttreatment PET/CT scan. Time zero is defined as completion of treatment.

Current evidence supports using PET/CT surveillance in patients with HNSCC with an initial complete response following definitive treatment.[9,11,14,23,24] Mehanna et al[11] recently demonstrated, in a multicenter prospective randomized controlled trial, that there was no statistical difference in 2-year overall survival between patients who underwent planned neck dissection versus those who underwent PET/CT-guided surveillance following definitive nonoperative therapy. However, imaging surveillance resulted in fewer operations and substantial cost savings for the nonoperative group.

Porceddu et al[14] prospectively investigated the performance of PET-directed management of the neck in 112 patients with node-positive HNSCC whose primary tumors showed complete response to therapy. The results of this study suggest that residual PET uptake is more relevant than a residual nodal mass in assessing therapy response. However, there was no difference in the TF rates between the patients with and without residual FDG avidity in our study (16% [13/82] versus 14% [4/28]). In our series, 9 of 51 patients (18%) with oropharyngeal cancer who had an IR developed locoregional failure within 2 years. More than 90% of patients in our series had TF within 5–16 months after the conclusion of treatment. Our results suggest that closer imaging and clinical surveillance in patients with an IR on initial PET/CT is warranted and may need to extend to 16 months to detect TF early with the goal of optimizing patient outcomes.

The TF rate of patients with NI-RADS 2 in our study is like that in the initial published performance of NI-RADS.[17] Krieger et al[17] analyzed a local recurrence rate of 58 of 618 targets that were scored NI-RADS 2. The overall rate of recurrence was 17.2%, with similar rates for the primary tumor bed and nodes. However, in our study, TF most frequently occurred in regional lymph nodes (65% [11/17]) versus the primary tumor site (41% [7/17]), with 1 patient having both local and regional recurrence. In addition, the results of our study reflect the capability of NI-RADS in predicting TF rates in patients with NI-RADS category 2. We support the current effort to standardize radiology reporting of PET/CT in patients with HNSCC with the goals of improving communication among physicians and guiding the next step in management.[16-18]

This study has several limitations. It is inherently limited by the retrospective study design resulting in variation in the timing of the first posttreatment PET/CT, which can impact the false-positive rate, mainly due to radiation-induced inflammation causing FDG avidity.[1,8] In our series, most patients had the first posttreatment PET/CT at 8–9 weeks, which has been shown to have an accuracy similar to that of PET/CT performed 11–14 weeks after treatment.[20] Regarding tumor staging, we used the *AJCC Cancer Staging Manual*, 7th edition, because of the heterogeneity of the clinical data and because it was used in the management of the patients. Approximately 15% of the patients with oropharyngeal cancer were also not tested for human papillomavirus status, limiting the application of the *AJCC Cancer Staging Manual*, 8th edition,[25] in some patients. Moreover, a standard uptake value analysis was not used in PET/CT interpretation;

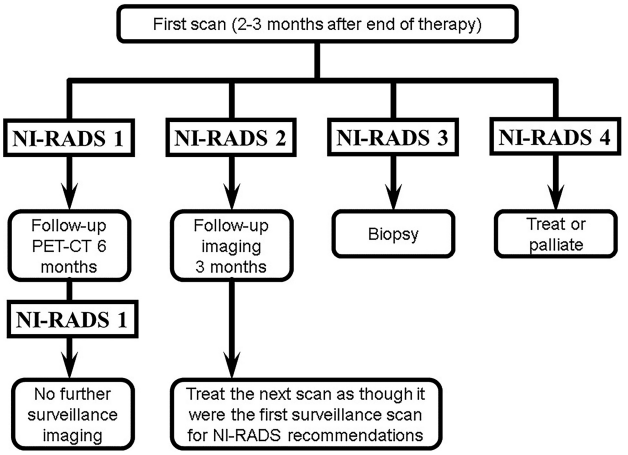

FIG 3. University of Pittsburgh PET/CT Surveillance Flowchart for Head and Neck Squamous Cell Carcinoma. NI-RADS 1 indicates no evidence of recurrence; NI-RADS 2, low suspicion; NI-RADS 3, high suspicion; NI-RADS 4, definitive disease recurrence.

however, the repeatability of quantitative standard uptake value measurements, particularly in lesions with low FDG uptake, has been proved to be poor,[26] and there is no established standard uptake value cutoff reliably distinguishing benign from malignant tissue. Furthermore, the true benefits of this PET/CT surveillance guideline for early detection of recurrent or residual disease and the potential impact on patients' overall survival require further investigation, preferably with an additional long-term prospective study. Last, our patients were derived from a single institution with extensive experience in PET/CT imaging of head and neck cancer; therefore, the results may not be universally applicable.

CONCLUSIONS

In patients with incomplete response (NI-RADS 2) after treatment of HNSCC, the NPV of the first posttreatment FDG-PET/CT was 85%, which was lower than the 91% NPV of FDG-PET/CT in patients with a complete response (NI-RADS 1). Patients with an incomplete response should undergo more frequent clinical and imaging surveillance than patients with a complete response.

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On-line Table: Characteristics of patients with treatment failure ($n = 17$)

Patient	Age (yr)/Sex	Primary Tumor Location	HPV Status	TNM Stage	Location of Recurrence	Histology Confirmation	Time Interval between TF and Treatment Completion (mo)	Adjuvant Treatment
1	47/M	Oropharynx	Unknown	T4aN2bM0	Nodes	Yes	12	Neck dissection
2	30/M	Oropharynx	Positive	T1N2bM0	Nodes	Yes	6	Neck dissection
3	48/M	Oropharynx	Positive	T1N2bM0	Nodes	Yes	11	Neck dissection
4	60/M	Oropharynx	Positive	T4aN1M0	Primary tumor	Yes	9	Partial glossectomy, tonsillectomy, neck dissection
5	62/F	Oropharynx	Negative	T3N0M0	Both primary tumor and nodes	No	13	Radiosurgery, chemotherapy
6	65/M	Oropharynx	Negative	T3N0M0	Primary tumor	Yes	10	Radiosurgery
7	69/M	Oropharynx	Positive	T2N1M0	Nodes	Yes	12	Neck dissection
8	69/F	Oropharynx	Negative	T4aN2cM0	Nodes	Yes	16	Neck dissection
9	61/M	Oropharynx	Positive	T3N2bM0	Primary tumor	Yes	5	Partial glossectomy, submandibulectomy, neck dissection
10	84/M	Oral cavity	Unknown	T4aN2cM0	Nodes	No	9	Radiosurgery, chemotherapy
11	43/M	Oral cavity	Unknown	T3N1M0	Nodes	Yes	5	Radiosurgery, chemotherapy
12	58/M	Oral cavity	Unknown	T2N2bM0	Nodes	No	13	Radiosurgery
13	58/M	Larynx	Unknown	T2N0M0	Primary tumor	Yes	8	Total laryngectomy, neck dissection
14	52/M	Larynx	Unknown	T3N2cM0	Primary tumor	No	7	Radiosurgery
15	46/M	Nasopharynx	Unknown	T2N1M0	Nodes	Yes	10	Neck dissection
16	63/M	Nasopharynx	Unknown	T2N0M0	Primary tumor	Yes	24	Chemoradiation
17	64/M	Hypopharynx	Unknown	T3N2bM0	Nodes	Yes	6	Total laryngectomy, neck dissection

Note:—HPV indicates human papillomavirus; TNM, Tumor, Node, Metastasis.