Negative Predictive Value of NI-RADS Category 2 in the First Posttreatment FDG-PET/CT in Head and Neck Squamous Cell Carcinoma

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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 respond 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
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 residual soft-tissue abnormality and/or FDG uptake 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 [18F] 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
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\% \((95\% \text{ CI}, 77\%–90\%)\). 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 \((63\%); 11/17\). 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 \((range, 5–24 \text{ months})\). The patients with residual FDG avidity had a TF rate like that in the patients who had no residual FDG avidity \((16\% [13/82] \text{ versus } 14\% [4/28])\).

There was no difference in predicting TF between NI-RADS 2 for the nodal site versus NI-RADS 2 for the primary tumor bed \((87\% \text{ versus } 86\%)\). Of the 110 patients, 51 patients were scored as having NI-RADS 2 due to IR of metastatic nodal disease \((P1N2 \text{ and } P2N2)\), 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 \((P2N1 \text{ and } P2N2)\), 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\%.\(^{19,20}\) 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\(^\text{16}\) 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).

### Patient characteristics \((N = 110)\)

| Characteristics | 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) | 13–97, 4.9, 4.4 |
| **Total patients with residual or recurrent disease within 2 yr after completion of primary chemoradiation therapy*** | 17/110 \((15\%)\) |

*NPV = 85\% \((95\% \text{ CI}, 77\%–90\%)\).
Current evidence supports using PET/CT surveillance in patients with HNSCC with an initial complete response following definitive treatment.\textsuperscript{9,11,14,23,24} Mehanna et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{17} Krieger et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{25} in some patients. Moreover, a standard uptake value analysis was not used in PET/CT interpretation;
however, the repeatability of quantitative standard uptake value measurements, particularly in lesions with low FDG uptake, has been proved to be poor, 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.

REFERENCES

1. King KG, Kositwattananark A, Genden E, et al. Cancers of the oral cavity and oropharynx: FDG PET with contrast-enhanced CT in the posttreatment setting. Radiographics 2011;31:355–73 CrossRef Medline
2. Tantiwongkosi B, Yu F, Kanard A, et al. Role of (18)F-FDG PET/CT in pre and post treatment evaluation in head and neck carcinoma. World J Radiol 2014;6:177–91 CrossRef Medline
3. Cheung PK, Chin RY, Elijk GD. Detecting residual/recurrent head and neck squamous cell carcinomas using PET or PET/CT: systematic review and meta-analysis. Otalaryngol Head Neck Surg 2016;154:421–32 CrossRef Medline
4. Sagardoy T, Fernandez P, Ghafouri A, et al. Accuracy of (18) FDG PET-CT for treatment evaluation 3 months after completion of chemoradiotherapy for head and neck squamous cell carcinoma: 2-year minimum follow-up. Head Neck 2016;38(Suppl 1):E1271–76 CrossRef Medline
5. Sheikhhabaei S, Taghipour M, Ahmad R, et al. Diagnostic accuracy of follow-up FDG PET or PET/CT in patients with head and neck cancer after definitive treatment: a systematic review and meta-analysis. AJR Am J Roentgenol 2015;205:629–39 CrossRef Medline
6. Chen SW, Hsieh TC, Yen KY, et al. Interim FDG PET/CT for predicting the outcome in patients with head and neck cancer. Laryngoscope 2014;124:2732–38 CrossRef Medline
7. Koshkareva Y, Branstetter BF 4th, Gaughan JP, et al. Predictive accuracy of first post-treatment PET/CT in HPV-related oropharyngeal squamous cell carcinoma. Laryngoscope 2014;124:1843–47 CrossRef Medline
8. Ho AS, Tsao GJ, Chen FW, et al. Impact of positron emission tomography/computed tomography surveillance at 12 and 24 months for detecting head and neck cancer recurrence. Cancer 2013;119:1349–56 CrossRef Medline
9. Meerwein CM, Queiroz M, Kollia S, et al. Post-treatment surveillance of head and neck cancer: pitfalls in the interpretation of FDG PET-CT/MRI. Swiss Med Wkly 2015;145:w14116 CrossRef Medline
10. McDermott M, Hughes M, Rath T, et al. Negative predictive value of surveillance PET/CT in head and neck squamous cell cancer. AJNR Am J Neuroradiol 2013;34:1632–36 CrossRef Medline
11. Mehanna H, Wong WL, McConkey CC, et al. PET-NECK Trial Management Group. PET-CT surveillance versus neck dissection in advanced head and neck cancer. N Engl J Med 2016;374:1444–54 CrossRef Medline
12. Chen YJ, Rath T, Mohan S. PET-computed tomography in head and neck cancer: current evidence and future directions. Magn Reson Imaging Clin N Am 2018;26:37–49 CrossRef Medline
13. Nayak JV, Walvekar RR, Andrade RS, et al. Deferring planned neck dissection following chemoradiation for stage IV head and neck cancer: the utility of PET-CT. Laryngoscope 2007;117:2129–34 CrossRef Medline
14. Porceddu SV, Pryor DI, Burmeister E, et al. Results of a prospective study of positron emission tomography-directed management of residual nodal abnormalities in node-positive head and neck cancer after definitive radiotherapy with or without systemic therapy. Head Neck 2011;33:1675–82 CrossRef Medline
15. Brizel DM, Prosnitz RG, Hunter S, et al. Necessity for adjuvant neck dissection in setting of concurrent chemoradiation for advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2004;58:4118–23 CrossRef Medline
16. Aiken AH, Farley A, Baugnon KL, et al. Implementation of a novel surveillance template for head and neck cancer: neck imaging reporting and data system (NI-RADS). J Am Coll Radiol 2016;13:743–46 CrossRef Medline
17. Krieger DA, Hudgins PA, Nayak GK, et al. Initial performance of NI-RADS to predict residual or recurrent head and neck squamous cell carcinoma. AJNR Am J Neuroradiol 2017;38:1193–99 CrossRef Medline
18. Aiken AH, Hudgins PA. Neck imaging reporting and data system. Magn Reson Imaging Clin N Am 2018;26:53–62 CrossRef Medline
19. Edge SB, Byrd DR, Compton CC, et al. AJCC cancer staging manual. 7th ed. New York: Springer; 2010:21–100
20. Leung AS, Rath TJ, Hughes MA, et al. Optimal timing of first posttreatment FDG PET/CT in head and neck squamous cell carcinoma. Head Neck 2016;38(Suppl 1):E853–58 CrossRef Medline
21. Newcombe RG. Statistical applications in orthodontics, Part II: confidence intervals for proportions and their differences. J Orthod 2000;27:339–40 CrossRef Medline
22. Adelstein D, Gillison ML, Pfister DG, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 2.2017. J Natl Compr Canc Netw 2017;15:761–70 CrossRef Medline
23. Sjövall J, Chua B, Pryor DI, et al. Long-term results of positron emission tomography-directed management of the neck in node-positive head and neck cancer after organ preservation therapy. Oral Oncol 2015;51:260–66 CrossRef Medline
24. Bird T, Barrington S, Thavaraj S, et al. (18)F-FDG PET/CT to assess response and guide risk-stratified follow-up after chemoradiotherapy for oropharyngeal squamous cell carcinoma. Eur J Nucl Med Mol Imaging 2016;43:1239–47 CrossRef Medline
25. Amin AB, Edge SB, Greene FL, et al. AJCC cancer staging manual. 8th ed. New York: Springer; 2017:55–184
26. de Langen AJ, Vincent A, Velasquez LM, et al. Repeatability of 18F-FDG uptake measurements in tumors: a metaanalysis. J Nucl Med 2012;53:701–08 CrossRef Medline