Journal of Nuclear Medicine, published on September 2, 2022 as doi:10.2967/jnumed.122.264424

Title: ^{18}F FDG PET/CT Prediction of Treatment Outcomes in HPV-positive, Locally Advanced Oropharyngeal Cancer Receiving De-intensified Therapy: Results from NRG-HN002

Short Running Title: PET/CT negative predictive value in NRG-HN002

Authors:
Rathan M. Subramaniam, MD, PhD, MPH, MBA [1,2], Lyudmila DeMora, MS [3], Min Yao, MD [4], Sue S. Yom, MD, PhD [5], Maura Gillison, MD, PhD [6], Jimmy J. Caudell, MD, PhD [7], John Waldron, MD [8], Ping Xia, PhD [9], Christine H. Chung, MD [7], Minh Tam Truong, MD [10], Michelle Echevarria, MD [7], Jason W. Chan, MD[5], Jessica L. Geiger, MD[11], Loren Mell, MD[12], Samantha Seaward, MD [13], Wade L. Thorstad, MD [14], Jonathan Jay Beitler, MD, MBA, FACR, FASTRO [15], Khalil Sultanem, MD, FRCP[16], Diagjin Blakaj, MD, PhD[17], Quynh-Thu Le, MD, FACR, FASTRO [18]

Affiliations:
1 Otago Medical School, University of Otago, New Zealand
2 Duke University, Durham, North Carolina
3 NRG Oncology Statistics and Data Management Center
4 University Hospitals Cleveland, Cleveland, Ohio
5 University of California, San Francisco, San Francisco, California
6 University of Texas MD Anderson Cancer Center, Houston, Texas
7 Moffitt Cancer Center, Tampa, Florida
8 Princess Margaret Hospital, Toronto, Oneida, Canada
9 Cleveland Clinic, Cleveland, Ohio
10 Boston Medical Center, Boston, Massachusetts
11 Case Western Reserve University, Cleveland, Ohio
12 UC San Diego Moores Cancer Center, San Diego, California
13 Kaiser Permanente NCI Community Oncology Research Program, Vallejo, California
14 Washington University School of Medicine, St. Louis, Missouri
15 Emory University/Winship Cancer Institute, Atlanta, Georgia
16 Jewish General Hospital, Montreal, Canada
17 Ohio State University Comprehensive Cancer Center, Columbus, Ohio
18 Stanford University, Stanford, California

Corresponding author:
Rathan M. Subramaniam
MD, PhD, MPH, MBA, FAUR, FRANZCR, FACNM, FSNMMI

Otago Medical School,
201 Great King Street,
Dunedin, New Zealand.
E mail: rathan.subramaniam@otago.ac.nz

Disclosure: Dr. ‘s Beitler, Blakaj, DeMora, Chan, Echevarria, Seaward, and Subramaniam have nothing to disclose. Dr. Caudell reports grants and honoraria rom Varian Medical Systems; honoraria from Galera. Dr. Chung reports participation on the Advisory Board for Bristol-Myers Squibb, CUE, Sanofi, Mirati, Merck, Brooklyn ImmunoTherapuetics, and Exelixis. Dr. Geiger reports consulting fees from Merck, Exelis, and Regeneron. Dr. Gillison reports grants from Kura Oncology, Agenus, Genocea Biosciences, Inc., Roche, and Bristol Myers Squibb; consulting fees from Kura Oncology, Shattuck Labs, Inc., Nektar Therapeutics, Ispen Biopharmaceuticals Inc., EMD Serono, Inc., Gilead Sciences, Inc., Eisai Medical Research Inc., Istari Oncology, Inc., LLX Solutions, LLC.,Onclive, Seagen, Debiopharm, Mirati Therapeutics, Sensei Biotherapeutics, Inc, BioNTech AG, and Coherus; participation on the Advisory Board for Kura DSMB,
SQZ Biotech, and BioMimetix; stock options from Sensei. Dr. Mell reports grants from RADIATION THERAPY ONCOLOGY GROUP FOUNDATION, Merck Sharp & Dohme Corp, SYNEOS HEALTH INC, and NCI; consulting fees from Cel-Sci. Dr. Le reports consulting fees from Nanobiotix, Roche, and Coherus; honoraria from Johns Hopkins, 2021 China
International Exchange and Promotive Association for Medical and Health Care (CPAM), Nasopharyngeal Cancer Branch Inaugural Conference and Minimally Invasive Surgery Training Course of Nasopharyngeal Cancer.

Clinical Trial Registration: NCT02254278

Abstract

Objective:

To determine the negative predictive value (NPV) of a 12-14 week post-treatment PET/CT for 2-year progression-free survival (PFS) and locoregional control (LRC) in patients with p16-positive locoregionally advanced oropharyngeal cancer (LA-OPC). Study was a secondary endpoint in NRG-HN002, a non-comparative phase II trial in p16-positive LA-OPC, stage T1-T2, N1-N2b or T3, N0-N2b (AJCC, 7th ed.) and ≤ 10 pack-year smoking. Patients were randomized in a 1:1 ratio to reduced-dose IMRT with or without cisplatin.

Methods:

PET/CT scans were reviewed centrally. Tumor response evaluations for the primary site, right neck, and left neck were carried out using a 5-point ordinal scale (Hopkins Criteria). Overall scores were then assigned as 'Negative,' Positive,' or 'Indeterminate'. Patients with a 'Negative' score for all three evaluation sites were given an overall score of 'Negative.' The hypotheses were NPV for PFS and LRC at two years post-treatment ≤ 90% vs >90% (1-sided alpha 0.10).

Results:

There were 316 patients enrolled, of whom 306 were randomized and eligible. Of these, 131 (42.8%) patients consented to a post-therapy PET/CT, and 117 (89.3%) patients were eligible for PET/CT analysis. The median time from the end of treatment to PET/CT scan was 94 days (range 52-139). Estimated 2-year PFS and LRC rates in the analysis subgroup were 91.3% (95% confidence interval CI [84.6, 95.8%]) and 93.8% (95% CI [87.6, 97.5%]), respectively. Post-treatment scans were negative for residual tumor for 115 patients (98.3%) and positive for two

patients (1.7%). NPV for 2-year PFS was 92.0% (90% lower confidence bound [LCB] 87.7%; p=0.30) and for LRC was 94.5% (90% LCB 90.6%; p=0.07).

Conclusion:

In the context of deintensification with reduced-dose radiation, the NPV of a 12-14 week post-therapy PET/CT for 2-year LRC is estimated to be > 90%, similar to that reported for patients receiving standard chemoradiation. However, there is insufficient evidence to conclude that the NPV is > 90% for PFS.

Keywords: PET/CT negative predictive value, p16-positive oropharyngeal cancer, NRG-HN002

Introduction

Head and neck squamous cell cancer (HNSCC) is the 9th most common malignant tumor worldwide, responsible for about 2% of all cancer related deaths[1]. Human papillomavirus (HPV)-associated HNSCC is rising in incidence and affects a younger population[2, 3]. This sub-group of patients harbors HPV in their tumor cells, predominantly HPV-16, and the tumors occur mostly in the oropharynx. The prognosis for these patients is better, with overall survival (OS) at three years being about 82% in locally advanced HPV positive HNSCC[4]. Standard therapy for locoregionally advanced oropharyngeal SCC (OPSCC) is a combination of 70 Gy radiation therapy (RT) and concurrent platinum chemotherapy[5]. Due to better survival outcomes in the HPV-associated OPSCC patient population and to reduce treatment-related short and long-term toxicities, various de-intensification treatment strategies are currently being explored[6, 7] for patients with HPV-associated OPSCC.

^{18}F FDG PET/CT has been shown to be a valuable imaging test in assessing treatment response in HNSCC. In a phase III randomized controlled study (n = 564), an ^{18}F FDG PET/CT-based surveillance strategy was non-inferior in survival and also cost-effective when compared to routine neck dissection[8], post standard CRT. Therefore, an ^{18}F FDG PET/CT is recommended to be performed, usually about 12 weeks or later from completion of CRT[9], to minimize false-positive results from radiation induced inflammation.

The five-point Hopkins Criteria for post-therapy ^{18}F FDG PET/CT interpretation was established and validated to standardize the interpretation and reduce variability[10]. Its reported accuracy is 86.4% (95% CI [79.3%, 91.3%]) with a negative predictive value of 92.1% (95% CI [86.9%, 95.3%])[9]. The Hopkins scale is a standardized qualitative interpretation

method designed for routine clinical practice. It has been recently shown to be equivalent in its performance compared to a more complex quantitative assessment method[11]. It also predicts survival outcomes, both OS and progression-free survival (PFS) in HNSCC patients[9, 10].

The Hopkins Criteria was internally and externally validated[9, 10] using mixed patient populations of HPV-positive and HPV-negative HNSCC. This study evaluates its performance metrics in HPV-positive, locally advanced oropharyngeal cancer patients receiving de-intensified therapy. Specifically, we determine the negative predictive value (NPV) of 12-14 week post-treatment ^{18}F FDG PET/CT for PFS and locoregional control (LRC) at two years in this population.

Patients and Methods

NRG-HN002 is a multi-institutional, non-comparative randomized phase II clinical trial (ClinicalTrials.gov identifier: NCT02254278). The trial determined the acceptability of two curative-intent strategies incorporating reduced-dose RT with or without cisplatin. This trial was designed to select the arm(s) meeting PFS (primary objective) and swallowing-related quality of life (QOL) criteria (as measured by the M.D. Anderson Dysphagia Inventory, MDADI; co-primary objective) for advancement to a definitive trial. The trial design, patients, inclusion/exclusion criteria, trial oversight, and definitions have already been described [6].

^{18}F FDG PET/CT Sub-study and Patients

All patients eligible for NRG-HN002 were offered to participate in an optional study to assess treatment response at two years based on 12-14 week post-treatment FDG PET/CT scans. Of the 306 eligible patients for the parent study, 131 consented to participate. Of these, 117 patients received protocol treatment and had acceptable quality scans and thus were eligible

for analysis. Fourteen patients were excluded from these analyses (1 did not receive protocol treatment, one had the scan in the wrong format, and 12 had no scan).

^{18}F FDG PET/CT Imaging

All sites were instructed to follow an ^{18}F FDG PET/CT imaging protocol. A serum glucose level of < 200mg/dl before the study, an uptake time of 60 min +/- 10 min, and dedicated head and neck (orbits to the upper thorax) and whole-body (orbits to upper thigh) acquisitions were obtained. Recommended PET acquisition parameters were six-bed positions and an acquisition of 2 to 5 minutes per bed position. The dedicated head and neck PET/CT typically followed the body exam. It included two bed positions (6 minutes per bed position), and the images were reconstructed into a 30 cm field of view (FOV) with a 256 x 256 matrix. The recommended acquisition parameters for the low dose CT scan were as follows: kV = 120; effective mAs = 90-150; gantry rotation time < 0.5 sec; maximum reconstructed slice width = 2.5 mm (overlap acceptable); standard reconstruction algorithm, maximum reconstruction diameter = 30 cm; and without iodinated contrast. The PET/CT data were corrected for dead time, scatter, randoms, and attenuation using standard algorithms provided by the scanner manufacturers. For the dedicated head and neck views, a post-filter with a full-width at half maximum (FWHM) in the range of 5 mm was recommended.

^{18}F FDG PET/CT Image Interpretation: Hopkins Criteria

PET/CT scans were reviewed both centrally and locally by participating institutions. Tumor response evaluations for the primary site, right neck, and left neck were carried out using a 5-point ordinal scale (Hopkins Criteria)[10]: Score 1-Definite complete metabolic response, Score 2-Likely complete metabolic response, Score 3-Likely inflammatory, Score 4-Likely residual

metabolic disease, and Score 5-Definite residual metabolic disease. A score of one or two was interpreted as negative, three as indeterminate, and four or five as positive. An overall score was assigned using this collapsed three-point categorization, with the highest score at any anatomic site determining the overall score.

In the central review, if at least one evaluation site was positive, the assigned overall score was positive. Patients with a negative score for all three evaluation sites were given an overall score of negative. This is a visual, qualitative analysis using IJV and liver uptake as internal controls.

In the local review, six patients had at least one evaluation site as positive and were assigned an overall positive score; one patient had a site score of positive and was given an overall score of indeterminate. Seven patients had site and overall scores of indeterminate; three patients had a site score of indeterminate and were ultimately given an overall score of negative. Patients with a negative score for all three evaluation sites were all given an overall score of negative.

Statistical Analysis

Distributions of patient's characteristics for those who did and did not consent to PET/CT imaging were compared using the Chi-square test with a significance level of 0.05. Hazard ratios (HRs) for PFS and locoregional failure (LRF) for these two subgroups were estimated using Cox proportional hazards models. Primary analyses included eligible patients who consented to PET/CT imaging and had a post-treatment PET/CT scan submitted for analysis regardless of timing. Sensitivity analyses included patients with scans 10-16 weeks post end of radiation therapy. Overall central scan review results were used in the primary analyses of the NPV. Level

of agreement between overall local and central PET/CT reads on the 3-point scale was assessed using percent agreement and Brennan-Prediger's (BP) and Gwet's coefficients. Level of agreement for primary site, right neck, and left neck scores was measured using the weighted versions of the same coefficients with linear weights to account for different levels of disagreement between categories of Hopkins criteria.

The primary purpose of analyzing FDG-PET/CT in NRG-HN002 is to determine the NPV of 12-14 weeks post-therapy FDG-PET/CT for 2-year PFS and 2-year LRC. Failure for PFS endpoint was defined as local, regional, or distant progression or death due to any cause; rates were calculated by the Kaplan-Meier method. The locoregional failure (LRF) endpoint was defined as local or regional progression, salvage surgery of the primary tumor with tumor present/unknown, salvage neck dissection with tumor present/unknown > 20 weeks after the end of radiation therapy, death due to study cancer without documented progression, or death due to unknown causes without documented progression; rates were calculated by the cumulative incidence method.

NPV was calculated as the proportion of PET/CT-negative patients who remained progression-free at two years and, separately, for those who maintained LRC (remained free of LRF) at two years. The binomial NPV estimates and exact confidence intervals (CI) were calculated. The null hypothesis of NPV ≤ 90% for PFS was tested against the alternative of NPV > 90% with a 1-sided binomial test at the 0.10 level. The power for these hypotheses was calculated under the alternative hypothesis of 95% NPV. With an estimated 140 available scans, the statistical power to reject the null hypothesis of NPV ≤ 90% was 76% per protocol-specified design.

Role of the Funding Source

NRG Oncology was responsible for data collection, statistical analysis, study design, and manuscript preparation. The National Cancer Institute sponsored the study. No commercial support was provided. The first author (R.M.S) had full access to all imaging data and the final responsibility to submit for publication. This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA180803 (IROC), UG1CA189867 (NRG Oncology NCORP) from the National Cancer Institute (NCI). This project is funded, in part, under a grant with the Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analyses, interpretations or conclusions.

Results

Patients

NRG-HN002 opened to accrual on October 27, 2014 and completed accrual on February 7, 2017 with 316 patients enrolled, of whom 308 were randomized (306 eligible). A total of 117 patients consented and were eligible for PET/CT analysis (Figure S1).

Table S1 summarizes patient and tumor characteristics by PET/CT consent status. Overall, 131 eligible patients (42.8%) consented to the post-therapy PET/CT exam. The consent rate was comparable between arms. No significant differences in patient and tumor characteristics were found between consent status groups.

Figure S2 summarizes the PFS analysis by consent status. The estimated HR (no consent vs. consent) is 1.77 (95% CI [0.91, 3.41]). Figure S3 summarizes the LRF analysis by consent status; the estimated HR (no consent vs. consent) is 1.41 (95% CI [0.65, 3.09]).

Patient and Tumor Characteristics

Of 131 patients who consented to PET/CT imaging, 117 (89.3%) were eligible for analysis. Table S2 shows patient and tumor characteristics for these patients. Median age is 62 years (min-max 39-84); 87.2% of patients are male, 90.6% are white, 81.2% have Zubrod performance status 0, 54.7% have tonsil primary site, 64.1% have T2-3 disease, 76.9% have N2 disease, and 79.5% had bilateral RT planning. The mean time from the end of treatment to the PET/CT scan is 13.6 weeks (standard deviation=1.9 weeks, range and interquartile range 7.4-19.8 and 12.7-14.4 weeks, respectively).

Study Endpoints

PET/CT Central Review

Table S3 summarizes the PET/CT scan central review results. Three patients had a site score of indeterminate but were ultimately given an overall score of negative. Overall, post-treatment scans for 115 of 117 patients (98.3%) were negative for residual tumor, and 2 (1.7%) were positive for residual tumor. For the primary site, post-treatment scans for 113 patients (96.6%) had 'definite complete metabolic response'; one patient (0.9%) had 'likely complete metabolic response'; two patients (1.7%) were assessed as 'likely inflammatory'; one patient (0.9%) had 'definite residual metabolic disease.' Similar results were found for the right and left neck (Table S3).

Negative Predictive Value of PET/CT for 2-year PFS

Table 1 summarizes the results for NPV for PFS at two years using central review results. Overall, the NPV for 2-year PFS is 92.0% (90% lower confidence bound [LCB] 87.7%; 95% confidence interval [CI] [85.4%, 96.3%]) with p=0.3 not rejecting the null hypothesis of the NPV for 2-year PFS ≤ 90%. With p > 0.10, these results indicate that there is not enough evidence to conclude that the NPV of PET/CT for 2-year PFS is > 90%, but were able to (with a 90% confidence) rule out an NPV below 87.7%. Comparable NPV results were found by treatment arm. On the IMRT+Cisplatin and IMRT arms, 57 and 58 patients are evaluable for NPV for PFS, respectively; one patient on each arm was censored for PFS. For patients with an overall PET/CT score of "positive for residual tumor," one patient (50.0%) had a failure for 2-year PFS, and one patient (50.0%) did not have failure for 2-year PFS (Table 1).

A sensitivity analysis to estimate the NPV was completed using evaluable patients with PET/CT scans completed 10-16 weeks post-radiation therapy. A total of 104 patients were included with a resulting overall NPV for 2-year PFS equal to 92.2% (90% LCB 87.6%; 95% CI [85.1%, 96.6%]) and p=0.3. Again, given p > 0.10, there is not enough evidence to conclude that NPV of PET/CT for 2-year PFS is > 90% (Table S4).

Negative Predictive Value of PET/CT for 2-year LRC

Table 2 summarizes the results for NPV for LRC at two years using central review results. The NPV for 2-year LRC is 94.5% (90% LCB 90.6%) with p = 0.07 rejecting the null hypothesis of the NPV for 2-year LRC ≤ 90% in favor of the alternative hypothesis of NPV > 90%. A 90% lower confidence bound for the NPV for 2-year LRC is 90.6%, a number above the hypothesized (null) NPV of 90% (95% CI [88.5%, 98.0%]). The NPV for 2-year LRC for the IMRT+Cisplatin arm is

94.6% (90% LCB 88.5%). The NPV for 2-year LRC for the IMRT arm is 94.4% (90% LCB 88.0%). Results by the treatment arm are also shown in Table 2. Of the 58 patients on the IMRT+Cisplatin arm eligible for PET/CT analysis, 56 are evaluable for NPV for LRC; two patients were censored for LRC prior to the 2-year time point. Of the 59 patients on the IMRT arm eligible for PET/CT analysis, 56 are evaluable for NPV for LRC; three patients were censored for LRC prior to the 2-year time point. For patients with an overall PET/CT score of "positive for residual tumor," one patient (50.0%) had failure for 2-year LRC, one patient (50.0%) did not have failure for 2-year LRC.

A sensitivity analysis to estimate the NPV was completed using evaluable patients with PET/CT scans completed 10-16 weeks post-radiation therapy. A total of 101 patients were included with a resulting overall NPV for 2-year LRC equal to 94.9% (90% LCB 90.8%; 95% CI [88.6%, 98.3%]) and p=0.06 again rejecting the null hypothesis of the NPV for 2-year LRC $\leq$ 90% in favor of the alternative hypothesis of NPV > 90% (one-sided alpha level 0.10) (Table S5).

PET/CT Local Assessment

Using local assessment results, the NPV for 2-year PFS is 91.8% (90% LCB 86.5%); 95% CI [83.8%, 96.6%]; p=0.4> 0.10). The NPV for 2-year LRC is 95.1% (90% LCB 90.5%]; 95% CI [88.0%, 98.7%]); p=0.08<0.10). Therefore, there is evidence that the NPV>90% for 2-year LRC. Results from the sensitivity analysis, using only scans completed 10-16 weeks post-radiation therapy, are similar for both endpoints (Tables S6 and S7).

Local and central assessments by neck site and overall are shown in Tables S8.1 and S8.2. The percent agreement, BP and Gwet's agreement coefficient between overall local and central

interpretation were 0.87 (95% CI [0.80, 0.94]), 0.80 (95% CI [0.70, 0.91]), and 0.86 (95% CI [0.78, 0.94]), respectively; Table S8.3. Agreement coefficient estimates for primary site, right and left neck are also shown in Table S8.3 These values suggest substantial agreement between local and central PET/CT interpretation for overall, primary site, left and right neck. Disagreements mainly consisted of patients who were classified with a definite metabolic disease by central reviews but were assigned a likely complete metabolic response or likely inflammatory by local assessments.

Discussion

In this study, testing a reduced dose of radiation therapy for patients with p16-positive, T1-T2 N1-N2b M0, or T3 N0-N2b M0 OPSCC (7th edition staging) with ≤10 pack-years of smoking, we estimated the performance characteristics of the Hopkins Criteria for the predictive ability of 12-14 weeks post-treatment ^{18}F FDG PET/CT for patient outcomes at two years. Based on the central review, most post-treatment scans (98.3%) were negative for residual tumor, and the NPV for LRC was 94.5%, and PFS was 92.0%. Similar NPVs were obtained based on local site analysis.

The study population of this trial had a distinctly more favorable outcome profile than the study population of the original development and internal [10] and subsequent external validation[9] of the Hopkins Criteria for interpretation of the 12-14 week post-treatment ^{18}F FDG PET/CT. The study population from the original derivation study (n=214) included many subsites of HNSCC patients (oropharynx 63.1%, oral cavity 5.1%, larynx 18.7%, and other sites 13.1%; 57.5% HPV positive) who had higher progression and death rates (median follow up of

27 months; 17.7% died and 29.4% had progression). The external validation study (ECLYPS) had a similar study population to the original derivation study, including various subsites (oropharynx 54.7%, oral cavity 6.3%, larynx 16.8% and other sites 22.2%; 29.6% HPV positive) and poorer outcome rates (13.6% died and LRF 20.8% at two years). Compared to these two study populations, the NRG-HN002 population analyzed in this sub-study included only patients with HPV-positive oropharyngeal cancer, and two-year PFS was 87.6% or above, and OS was 96.7% or above. Hence, this trial provides the performance characteristic (NPV) of the Hopkins Criteria for post-treatment ^{18}F FDG PET/CT in a favorable de-intensified outcome group.

One of the Hopkins Criteria characteristics is decreasing the number of intermediate readings and uncertainty about inflammatory uptake. The number of patients with intermediate score (score 3, likely inflammatory) were low in this study (n = 1 for left neck, n = 0 for right neck, and n = 2 for the primary site), which is similar to the prior studies[9, 12-14]. This is most likely due to the standardized qualitative reads and subsiding radiation-induced inflammation by 12-14 weeks post-therapy. Compared to other interpretation criteria (such as NI-RADS, Porceddu, Deauville), the Hopkins Criteria has been demonstrated to reduce the intermediate interpretation to the lowest[14]. In addition, unlike the prior studies, the number of patients with scores representing residual disease is extremely low (1.7%) in this study, compared to the other studies[9, 10], due to the favorable HPV[2] oropharyngeal SCC population in this study who responded well for the treatment.

This study establishes the value of Hopkins Criteria in a multi-center clinical trial setting. The advantage of standardized qualitative interpretation criteria is the ease and rapid deployment in clinical practice setting[15], while maintaining similar accuracy of

semiquantitative interpretation methods such as PERCIST[16] and other methods[11], which require more stringent standard methods of performing the scans and complex analyses. The analysis suggests substantial agreement between local and central interpretation for overall, primary site, left, and right neck interpretation. In future studies, the level of agreement could be further optimized by including a training program or training set for site reads. Further, the added value of performing a PET/CT three months post-therapy in a favourable population could be established by performing a clinical examination and therapy response judgement first, before doing a PET/CT. Then, comparing these results or revealing them to the clinical team and estimating the final clinical judgment at three months post-therapy. This would have demonstrated the true added value of performing a PET/CT to the clinical judgement, at this time point.

There are limitations to this secondary endpoint analysis of NRG-HN002. First, PET/CT was an optional method for therapy response assessment at the time this study was designed, and the actual sample size was slightly lower than the projected (113 vs 140 patients). Second, presumably higher risk patients did not opt-in for PET/CT. However, this apparent finding was not statistically significant and was not explained by differences in tumor and patient characteristics between participants and non-participants in the PET/CT substudy. Third, although the protocol specified a post-treatment PET/CT at 12-14 weeks, the actual PET/CT time varied around 12-14 weeks post-treatment. However, the sensitivity analysis, which included PET/CT scans done at 10-16 weeks post-treatment (89%), led to the same conclusions regarding NPV of PET/CT as the analysis using all scans. Four, our study was not designed to compare either clinical evaluation or CT imaging versus PET/CT imaging, so we cannot comment

on the relative adequacy of various follow-up methods in this low-risk group. Furthermore, NPV estimates close to 2-year PFS and LRC rates suggests that marginal additional information on 2-year post-treatment outcomes is gained by using PET/CT around 12-14 weeks post-treatment. However, as discussed above, this result alone should not be used to determine the adequacy of PET/CT in this population. Other metrics such as specificity, sensitivity, and positive predictive value should be considered; none of these metrics can be properly and accurately estimated from this substudy.

In conclusion, within the context of deintensification with reduced-dose radiation, the NPV around 12-14 week post-therapy PET/CT for 2-year LRC is statistically > 90%, similar to that reported for patients receiving standard chemoradiation. However, there is insufficient evidence to conclude that the NPV is > 90% for PFS.

Key Points:

QUESTION:

Determine the negative predictive value of 12-14 week post-treatment ^{18}F FDG PET/CT for progression free survival (PFS) and locoregional control (LRC) at two years in HPV-positive, Locally Advanced Oropharyngeal Cancer Receiving De-intensified Therapy.

PERTINENT FINDINGS:

NRG-HN002 is a multi-institutional, non-comparative randomized phase II clinical trial (ClinicalTrials.gov identifier: NCT02254278). The primary endpoint of the study was the NPV for PFS and LRC at two years. The NPV of around 12-14 weeks post-therapy PET/CT for 2-year LRC is statistically > 90%, similar to that reported for patients receiving standard chemoradiation. However, there is insufficient evidence to conclude that the NPV is > 90% for PFS.

IMPLICATIONS FOR PATIENT CARE:

FDG PET/CT performed around 12-14 weeks post-therapy has very high NPV for PFS and LRC in HPV-positive, locally Advanced Oropharyngeal Cancer Receiving De-intensified Therapy.

References

1. Siegel, R.L., et al., *Cancer Statistics, 2021.* CA Cancer J Clin, 2021. **71**(1): p. 7-33.
2. Gillison, M.L., et al., *Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma.* J Clin Oncol, 2015. **33**(29): p. 3235-42.
3. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* N Engl J Med, 2010. **363**(1): p. 24-35.
4. Sun, Y., et al., *Therapeutic strategies of different HPV status in Head and Neck Squamous Cell Carcinoma.* Int J Biol Sci, 2021. **17**(4): p. 1104-1118.
5. Bourhis, J., et al., *Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial.* Lancet Oncol, 2012. **13**(2): p. 145-53.
6. Yom, S.S., et al., *Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002).* J Clin Oncol, 2021. **39**(9): p. 956-965.
7. Strohl, M.P., K.C. Wai, and P.K. Ha, *De-intensification strategies in HPV-related oropharyngeal squamous cell carcinoma - a narrative review.* Ann Transl Med, 2020. **8**(23): p. 1601.
8. Mehanna, H., et al., *PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer.* N Engl J Med, 2016. **374**(15): p. 1444-54.
9. Van den Wyngaert, T., et al., *Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography After Concurrent Chemoradiotherapy in Locally Advanced Head-and-Neck Squamous Cell Cancer: The ECLYPS Study.* J Clin Oncol, 2017. **35**(30): p. 3458-3464.
10. Marcus, C., et al., *Head and neck PET/CT: therapy response interpretation criteria (Hopkins Criteria)-interreader reliability, accuracy, and survival outcomes.* J Nucl Med, 2014. **55**(9): p. 1411-6.
11. Helsen, N., et al., *Quantification of 18F-fluorodeoxyglucose uptake to detect residual nodal disease in locally advanced head and neck squamous cell carcinoma after chemoradiotherapy: results from the ECLYPS study.* Eur J Nucl Med Mol Imaging, 2020. **47**(5): p. 1075-1082.
12. Van den Wyngaert, T., S. De Schepper, and L. Carp, *Quality Assessment in FDG-PET/CT Imaging of Head-and-Neck Cancer: One Home Run Is Better Than Two Doubles.* Front Oncol, 2020. **10**: p. 1458.
13. Kendi, A.T., et al., *Head and neck PET/CT therapy response interpretation criteria (Hopkins criteria) - external validation study.* Am J Nucl Med Mol Imaging, 2017. **7**(4): p. 174-180.
14. Zhong, J., et al., *Post-treatment FDG PET-CT in head and neck carcinoma: comparative analysis of 4 qualitative interpretative criteria in a large patient cohort.* Sci Rep, 2020. **10**(1): p. 4086.
15. Peacock, J.G., C.T. Christensen, and K.P. Banks, *RESISTing the Need to Quantify: Putting Qualitative FDG-PET/CT Tumor Response Assessment Criteria into Daily Practice.* AJNR Am J Neuroradiol, 2019. **40**(12): p. 1978-1986.

16. Wahl, R.L., et al., *From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors.* J Nucl Med, 2009. **50 Suppl 1**: p. 122S-50S.

Table 1. Negative Predictive Value per Central Review for Two-Year Progression-Free Survival

	IMRT + Cisplatin	IMRT	Total
PET overall interpretation			
Positive for residual tumor	0 (0.0%)	2 (3.4%)	2 (1.7%)
Negative for residual tumor	57 (100.0%)	56 (96.6%)	113 (98.3%)
2-year progression-free survival status in PET negative			
Failure	4 (7.0%)	5 (8.9%)	9 (8.0%)
Non-failure	53 (93.0%)	51 (91.1%)	104 (92.0%)
NPV of 2-yr PFS	93.0%	91.1%	92.0%
(95% exact CI)	(83.0-98.1%)	(80.4-97.0%)	(85.4-96.3%)
(One-sided 90% exact LCB)	(86.5%)	(84.1%)	(87.7%)
H0: NPV ≤90% vs HA: NPV >90%			
p-value (exact)			0.2964

CI, confidence interval; LCB, lower confidence bound

Table 2. Negative Predictive Value per Central Review for Two-Year Locoregional Control

	IMRT + Cisplatin	IMRT	Total
PET overall interpretation			
Positive for residual tumor	0 (0.0%)	2 (3.6%)	2 (1.8%)
Negative for residual tumor	56 (100.0%)	54 (96.4%)	110 (98.2%)
2-year local-regional control status in PET negative			
Failure	3 (5.4%)	3 (5.6%)	6 (5.5%)
Non-failure	53 (94.6%)	51 (94.4%)	104 (94.5%)
NPV of 2-yr LRC	94.6%	94.4%	94.5%
(95% exact CI)	(85.1-98.9%)	(84.6-98.8%)	(88.5-98.0%)
(One-sided 90% exact LCB)	(88.5%)	(88.0%)	(90.6%)
H0: NPV ≤90% vs HA: NPV >90%			
p-value (exact)			0.0682

CI, confidence interval; LCB, lower confidence bound

Graphical Abstract