European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:794–800
https://doi.org/10.1007/s00259-019-4272-8

ORIGINAL ARTICLE

Post-radiotherapy PET/CT for predicting treatment outcomes in head and neck cancer after postoperative radiotherapy

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Received: 22 August 2018 / Accepted: 15 January 2019 / Published online: 24 January 2019

Abstract

Purpose The purpose of this study was to retrospectively review the role of post-treatment (post-tx) FDG-PET/CT scans in patients receiving postoperative intensity-modulated radiotherapy (IMRT) for head and neck squamous cell carcinomas (HNSCC).

Materials and methods Eighty-two patients with HNSCC treated with surgery and postoperative IMRT with or without chemotherapy from October 15, 2008 to December 31, 2014 that had post-tx PET/CT within 6 months of completing IMRT were included. PET/CT was considered positive based on multi-disciplinary review integrating clinical information. Survival analysis was performed using the Kaplan-Meier method. Categorical and continuous predictors of positive post-tx PET/CT were evaluated using Fisher's exact test and logistic regression, respectively. Predictors for survival outcomes were evaluated with log-rank testing. A $p \leq 0.05$ was considered statistically significant.

Results Median follow-up was 3.88 years. For all patients, 3-year overall survival (OS) and recurrence-free survival (RFS) were 71.8% and 61.3%, respectively. Patients with positive post-tx PET/CT had worse OS compared to those with negative post-tx PET/CT (log rank $p < 0.001$). For patients with positive post-tx PET/CT, 3-year OS was 11.2% compared to 89.9% for patients with negative post-tx PET/CT. The positive predictive value (PPV) of PET/CT was 100% for local recurrence (LR), regional recurrence (RR) and distant metastasis (DM). The negative predictive values (NPV) for LR, RR and DM were 89.0%, 89.2%, and 85.9%, respectively. Perineural invasion ($p = 0.009$), p16 status ($p = 0.009$), non-oropharyngeal primary site ($p = 0.002$), and the use of chemotherapy ($p = 0.01$) were independent predictors of positive PET/CT.

Conclusions Post-tx PET/CT after postoperative radiation is prognostic for survival outcomes. The PPV of post-tx PET for recurrence was excellent, allowing for early detection of recurrent disease. Post-tx PET/CT should be considered after postoperative radiation.

Keywords Head and neck cancer · PET/CT · Prognostic factors · Postoperative radiotherapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy in the world. Patients with locally advanced disease are usually managed with one of two approaches: surgical resection followed by adjuvant radiotherapy or definitive radiotherapy with or without concurrent chemotherapy. After radiotherapy (RT), effective and reliable

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imaging is essential for the assessment of treatment response, survey for recurrence and for the determination of the need for early salvage in the case of residual or recurrent disease in the head and neck.

Post-treatment (post-tx) 18-fluorodeoxyglucose (^{18}FDG) positron emission tomography/computed tomography (PET/CT) has been used extensively after definitive radiotherapy in head and neck cancer, especially to assess treatment response and guide the need for neck dissection [1, 2]. Multiple studies have shown that if post-tx PET/CT demonstrates resolution of locoregional disease, patients may undergo observation rather than prophylactic neck dissection [3–11]. Further, negative post-treatment PET/CT after definitive radiotherapy is associated with excellent long-term prognosis [12].

Despite the preponderance of data in the definitive setting, there is little data examining the utility of post-tx PET/CT after surgical resection and adjuvant radiotherapy. At our institution, it is routine practice to obtain PET/CT 3 months after completing adjuvant radiotherapy. In this retrospective study, we present the long-term results of our institutional practice utilizing post-tx PET/CT after adjuvant radiotherapy in order to assess the utility of this imaging modality in this setting.

Materials and methods

Patient population

Patients with HNSCC treated with surgery and postoperative intensity-modulated radiotherapy (IMRT) with or without chemotherapy from October 15, 2008 to December 31, 2014, at the Department of Radiation Oncology, University Hospitals Cleveland Medical Center, with a post-tx PET/CT within 6 months of completing IMRT were eligible. Post-tx PET/CT is routinely obtained at our institution to assess the treatment response for all HNSCC patients who undergo surgery and adjuvant RT regardless of suspicion of recurrence. Patients who received definitive radiotherapy, had clinically evident recurrent disease, or had prior head and neck radiotherapy were excluded. This retrospective study received institutional review board approval at University Hospitals Cleveland Medical Center.

Radiotherapy and chemotherapy

All patients were treated with IMRT using either the TomoTherapy system with the proprietary treatment planning system or Elekta linear accelerators using the Pinnacle^3 treatment planning system. Areas of high-risk in the primary tumor bed and neck were treated to a total dose of 60–66 Gy in 2.0–2.2 Gy fractions, while elective areas of the neck received 50–56 Gy in 1.8–2.0 Gy fractions. Concurrent chemotherapy was delivered based on the presence of high-risk features such as extracapsular extension (ECE), positive margins or multiple lymph nodes after multidisciplinary discussion. The most common chemotherapy regimen was weekly cisplatin 40 mg/m^2.

Clinical PET/CT scanning

The examination was performed on a PET/CT system (Philips Healthcare) equipped with a time-of-flight (TOF) scanner. The patients fasted for at least 4 h, after which they received an injection of ^{18}FDG to a mean activity of 370 MBq (range: 296– 518). The CT consists of a 16-slice multi-detector helical CT and was performed before the PET scan. The CT data were used for generation of the CT transmission map, image fusion, and anatomical correlation with the PET findings. Head and neck images were acquired first with the arms down, and then images of the torso with arms up (if tolerated). The scans were acquired during normal breathing. No oral or intravenous contrast was administered. The parameters for the CT were based on institutional guidelines: 120 kVp, pitch of 0.829 and 100 mAs (patient weight < 150 lbs) or 150 mAs (patient weight ≥ 150 lbs), 5-mm slice thickness. The PET scanner has an active transverse field of view (FOV) of 57.6 cm. For PET scanning, the matrix size was 144 × 144, and the voxel size was 4 × 4 × 4 mm^3. The scan time/bed position was as follows: 1.5 min/bed, patient weight 100–150 lbs.; 2.0 min/bed, patient weight 151–200 lbs.; 2.5 min/bed, patient weight 201–300 lbs.; and 3.0 min/bed, patient weight > 300 lbs. The list-mode TOF algorithm and line-of-response TruFlight (LOR-TF) RAMLA method, so-called BLOB-OS-TF, were used for image reconstruction.

PET/CT image interpretation

PET/CT was reviewed and interpreted in a multi-disciplinary tumor board with the consensus opinion of the radiologist, radiation oncologist, and head and neck surgeons. The opinion relied on imaging integrated with clinical information. PET/CT scans with no focal increased uptake of FDG were interpreted as negative. PET/CT scans with increased FDG uptake considered to be physiologic or related to treatment effects were also interpreted as negative. Equivocal PET results or findings suspicious for tumor recurrence were interpreted as positive.

Statistical analysis

The positive predictive value (PPV) and negative predictive value (NPV) for post-tx PET/CT were calculated for any recurrence, local recurrence, regional recurrence, and distant metastasis (DM) for all patients. Overall survival and recurrence-free survival were calculated using the Kaplan–Meier product-limit method. The follow-up time was

calculated from the date of surgery to the date of last follow-up or death. Survival differences were calculated using the log-rank statistic. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed in R version 3.2.3 using the Survival package.

Results

Patient characteristics

Eighty-two patients were eligible with a median follow-up of 3.88 years (range: 0.46 – 7.26 years). Detailed patient and treatment characteristics are listed in Table 1. Twenty-one patients had oropharyngeal primaries and 61 patients had non-oropharyngeal primaries. Seventeen of 21 patients with oropharyngeal primaries had p16+ disease. Among patients with non-oropharyngeal primaries, 38 had oral cavity primaries, 13 had larynx primaries, seven had sinonasal primaries, one had a hypopharynx primary and two had an unknown primary. Eight patients with non-oropharyngeal primaries had p16+ disease (2 patients with sinonasal cancer, 3 patients with oral cavity cancer, 1 patient with larynx cancer and both patients with an unknown primary cancer).

The median interval of PET/CT from radiotherapy completion was 13.57 weeks (range: 7.86–25.57 weeks).

General outcomes

At last follow-up, 53 patients were alive. The 3-year overall survival and recurrence-free survival for the entire population are 71.8% and 61.3%, respectively (Fig. 1).

There were 33 patients who experienced failures. Two patients had local recurrence alone, three patients had regional recurrence alone and 11 patients had distant metastasis alone. Four patients had simultaneous local, regional and distant recurrence and seven patients had simultaneous local and regional recurrence without distant metastasis. Finally, four patients had a local recurrence with simultaneous distant metastasis without regional recurrence and two patients had regional recurrence with simultaneous distant metastasis without local recurrence.

Sixty-three patients had negative PET/CT and only 14 patients experienced failure after negative PET/CT. One patient had local recurrence alone, four patients had local recurrence with simultaneous regional recurrence alone, two patients had local recurrence with simultaneous distant recurrence alone and one patient had simultaneous local, regional and distant recurrence. No patients had an isolated regional recurrence. Six patients had isolated distant recurrence. The NPVs of post-tx PET/CT for local recurrence (LR), regional recurrence (RR) and distant metastases (DM) were 89.0%, 89.2%, and 85.9%, respectively.

Table 1 Baseline patient characteristics

Characteristic	Number of patients, *n* (%)
Age	
< 50	9 (11.0%)
50–59	17 (20.7%)
60–69	33 (40.2%)
≥ 70	23 (28.0%)
Sex	
Male	61 (74.4%)
Female	21 (25.6%)
Primary tumor site	
Oral cavity	38 (46.3%)
Oropharynx	21 (25.6%)
p16+	17 (81.0%)
p16-	4 (19.0%)
Larynx	13 (15.9%)
Sinus	7 (8.5%)
Hypopharynx	1 (1.2%)
Unknown primary	2 (2.4%)
Chemotherapy	
Yes	43 (52.4%)
No	39 (47.6%)
T-Stage	
rT0[a]	2 (2.4%)
T0 (unknown primary)	2 (2.4%)
T1	12 (14.6%)
T2	17 (20.7%)
T3	3 (3.7%)
T4	46 (56.1%)
N-Stage	
N0	26 (31.7%)
N1	9 (11.0%)
N2A	6 (7.3%)
N2B	33 (40.2%)
N2C	8 (9.8%)
Risk features	
Lymphovascular space invasion	32
Perineural invasion	34
Positive margins	4
Extranodal extension	25
Median treatment time (days)	44 (range: 38–61)

[a] These patients had a previous early stage oral tongue primary and developed isolated neck recurrence. They were treated with more surgery and postoperative radiotherapy

Nineteen patients had positive PET/CTs: nine had local findings, eight had regional findings, and 11 had distant findings. All findings were consistent with recurrent disease, and as such the PPV of post-tx PET/CT was 100% for local recurrence, regional recurrence and distant metastasis.

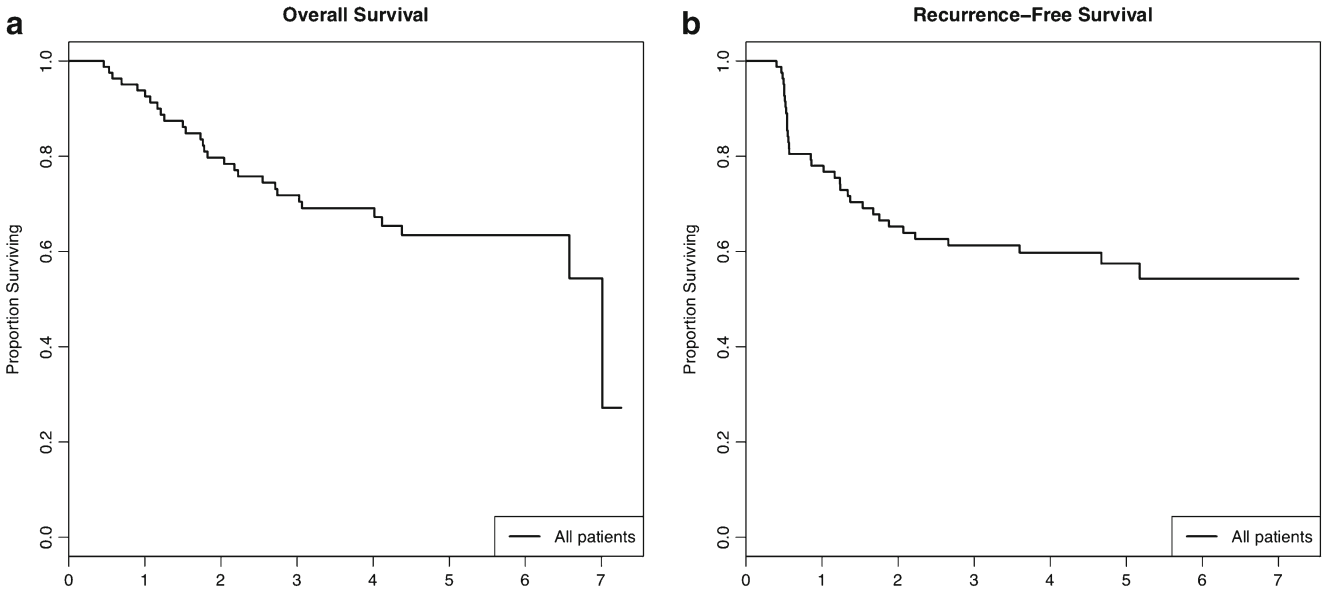

Fig. 1 Kaplan-Meier curve for overall survival and recurrence-free survival for entire population. The figure shows overall survival (**a**) and recurrence-free survival curves (**b**) for the overall population

Factors predictive of post-Tx PET/CT outcomes

To assess which patients may benefit from a post-tx PET/CT, univariate analysis was performed using pre-RT risk features (Table 2). On univariate analysis, perineural invasion ($p = 0.009$), the use of chemotherapy ($p = 0.01$), non-oropharyngeal primary site ($p = 0.002$) and p16 status ($p = 0.009$) were significantly associated with positive post-tx PET/CT. Extranodal extension trended towards predicting positive post-tx PET/CT ($p = 0.09$). Age, sex, lymphovascular space invasion, margin status and treatment time did not predict post-tx PET/CT outcomes.

Among 21 patients with an oropharyngeal primary, none had a positive post-tx PET/CT, and only one developed a recurrence. This single patient had p16 negative disease.

Among 61 patients with non-oropharyngeal primaries, 19 patients had a positive post-tx PET/CT. On subgroup analysis of patients with non-oropharyngeal primaries, the use of chemotherapy ($p = 0.02$) was associated with positive post-tx PET/CT, and perineural invasion ($p = 0.056$) trended towards an association with positive post-tx PET/CT. P16 status was not associated with post-tx PET/CT outcomes among patients with non-oropharyngeal primaries ($p = 0.41$).

Table 2 Univariate analysis of predictors of positive post-treatment PET/CT

Predictors	*p* value
Age	0.21
Gender	0.24
Lymphovascular space invasion	0.78
p16 negative	0.009
Perineural invasion	0.009
Positive margins	1.00
Extranodal extension	0.09
Use of chemotherapy	0.01
Non-oropharyngeal primary site	0.002
Treatment time	0.23

Prognostic implications of PET/CT

Post-tx PET/CT was prognostic for overall survival. Three-year overall survival for patients with a negative post-tx PET/CT was 89.9% compared to 11.2% for patients with a positive post-tx PET/CT (Fig. 2, $p < 0.001$). Examining only the subgroup of patients with non-oropharyngeal cancers, negative post-tx PET/CT remained strongly predictive of long-term survival (3-year OS: 84.3% versus 11.1% for positive post-tx PET/CT).

Discussion

Post-treatment PET/CT has had a significant impact in the management of locally advanced HNSCC after definitive RT, most notably in selecting patients for neck dissection [3–11]. The role of PET/CT after post-operative RT for HNSCCs is less well defined.

Importantly, our results have demonstrated that post-tx PET/CT is of excellent prognostic value after adjuvant radiotherapy in HNSCC. The 3-year OS after a negative post-tx PET/CT approaches 90% compared to just over 11% in patients with a positive post-tx PET/CT. The excellent long-term survival of patients with a negative post-tx PET/CT is

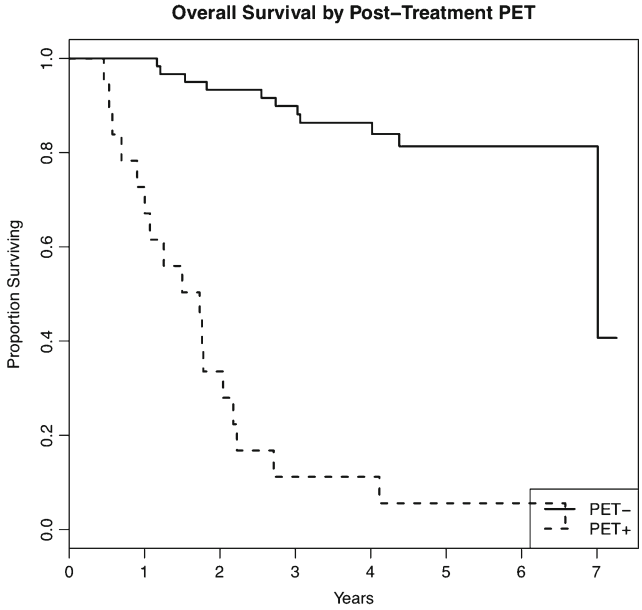

Fig. 2 Kaplan-Meier curve for overall survival stratified by the result of post-treatment PET/CT. There is a significant difference in 3-year overall survival for patients with a negative post-treatment PET/CT compared to those with a positive post-treatment PET/CT ($p < 0.001$)

reflective of the excellent NPVs of PET/CT for late local and regional recurrences, which in our series approach 90%, similar to values reported in the definitive setting [13]. Thus, patients with a negative post-tx PET/CT after surgery and adjuvant therapy less frequently develop disease recurrence. Conversely, the dismal long-term survival of patients with a positive post-tx PET/CT reflects the accuracy of PET/CT in early detection of recurrent disease and the aggressive nature of patients who have rapid recurrence after combination of surgery and radiotherapy.

Despite the poor outcomes in those who have recurrent disease, early detection of recurrent disease with PET/CT may make early surgical salvage possible in patients with resectable disease, or systemic treatment may be initiated earlier for those with unresectable recurrent disease. Emerging systemic therapies including immunotherapy may change these poor outcomes and lead to better long-term results in these patients [14–16].

Our reported PPVs for post-tx PET/CT were 100% for local and regional recurrences, much higher than the 50–60% reported in the definitive setting [13]. This is likely because no gross disease was present in this patient population prior to adjuvant therapy, eliminating false positives from residual inflammatory activity of slowly resolving disease [17]. Further, PET/CT data was reviewed and interpreted in a multi-disciplinary setting integrating clinical information rather than using a particular SUV cutoff as a threshold for positive disease. Thus, if there was PET uptake in a region that was not clinically suspicious for disease recurrence or reflecting asymmetric activity related to flap reconstruction, it would be deemed negative.

We also sought to investigate which clinical and pathologic features correlate with abnormal post-tx PET findings. We found that four features predicted for abnormal post-tx PET/CT after adjuvant radiotherapy: non-oropharyngeal primary site, p16 status, perineural invasion, and the use of chemotherapy. As the majority of oropharyngeal cancers in our series were p16+ while the majority of non-oropharyngeal cancers were p16 negative, it is likely that the significance of primary tumor site for predicting outcomes of post-tx PET/CT reflects the underlying differences in disease biology between p16+ and p16 negative disease [18]. Seventeen of 21 oropharyngeal cancer patients were p16+ and all oropharyngeal cancer patients had a negative post-tx PET/CT. Further, the single oropharyngeal cancer patient who developed a recurrence after a negative post-tx PET/CT was p16-. This suggests that PET/CT after adjuvant RT for p16+ oropharyngeal cancers may be omitted. Interestingly, on a subgroup analysis of non-oropharyngeal cancer patients, p16 status did not predict outcomes of post-tx PET/CT despite studies showing the favorable prognosis of p16 positivity in non-oropharyngeal cancers [19].

Among all patients, perineural invasion ($p = 0.009$) was associated with a higher rate of positive post-tx PET/CT, and this appeared to be confirmed by a trend in the subgroup of patients with non-oropharyngeal cancers ($p = 0.056$). This may reflect underlying aggressive disease biology as has been shown previously in mucosal head and neck cancers [20, 21]. Further, patients with perineural invasion may develop disease tracking along cranial nerves and thus may be more likely to develop disease recurrence outside the normal post-operative radiation field.

Surprisingly, other risk features typically associated with a higher risk of disease recurrence such as extranodal extension and positive margins were not significantly associated with an increased risk of positive post-tx PET/CT. However, it should be noted that patients with these features were more likely to receive concurrent chemotherapy based on the pooled results of EORTC 22931 and RTOG 9501 [22–24], a feature which was associated with an increased risk of positive post-tx PET/CT. Of the 27 patients in this series with either of these features, 24 (88.8%) received chemotherapy. Further, of the 43 patients that received chemotherapy, 24 (55.8%) had at least one of these high-risk features, compared to only 3 (7.7%) of the 39 patients who did not receive chemotherapy. Thus, the use of chemotherapy as a predictor of post-tx PET/CT is a surrogate for these high-risk features of recurrence. In this light, the lack of significance of these features individually may reflect inadequate patient numbers, particularly, with only four patients with positive margins in our cohort.

Finally, multiple authors have shown the value of PET/CT prior to adjuvant radiation for HNSCCs. Shintani et al. [25] reported suspicious findings in 26.4% of patients undergoing PET/CT prior to beginning adjuvant RT; 45.8% of the lesions

biopsied in their series demonstrated recurrent cancer. Similarly, both Liao [26] and Dutta [27] reported 24.1% and 31.8% rates of abnormal findings on PET/CT obtained before adjuvant RT, respectively. This raises the possibility that some of the recurrent disease found by post-tx PET/CT in our series may reflect recurrent disease that was present prior to the beginning of adjuvant radiotherapy. It is not routine practice to obtain a post-surgery restaging PET/CT at our institution, unless there is clinical suspicion of disease recurrence or significant delay prior to beginning adjuvant RT. However, all patients included in this series had no evidence of disease recurrence on RT planning imaging including contrast-enhanced CT.

Conclusion

Post-tx PET/CT after postoperative radiation is accurate in early detection of recurrent disease and is prognostic for long-term survival outcomes. More than half of recurrences were detected in the post-tx PET/CT obtained 3–6 months after adjuvant radiotherapy. Post-tx PET/CT should be considered after postoperative radiation, particularly in patients with perineural invasion.

Compliance with ethical standards

Conflict of interest Yan Li MD has no conflicts of interest. Musaddiq J. Awan MD has no conflicts of interest. Tangel Chang D.O. has no conflicts of interest. Pierre Lavertu MD has no conflicts of interest. Chad Zender MD has no conflicts of interest. Rod Rezaee MD has no conflicts of interest. Nicole Fowler MD has no conflicts of interest. Jay Wasman MD has no conflicts of interest. Norbert Avril, MD has no conflicts of interest. Nianyong Chen, MD PhD has no conflicts of interest. Mitchell Machtay MD reports that he is a consultant for Bristol-Myers, Abbvie and Novocure. Min Yao MD PhD has no conflicts of interest.

Ethical approval This is a retrospective, minimal risk study. Institutional review board approval was obtained for retrospective review of patient charts. This was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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