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Positron Emission Tomography for Neck Evaluation Following Definitive Treatment with Chemoradiotherapy for Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

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Abstract

Objectives—The objective of the current review was to assess published data on the role of Positron Emission Tomography (PET) for evaluation of nodal residual disease after definitive chemoradiotherapy for head and neck squamous cell carcinoma (HNSCC).

Methods—Studies were identified by searching PubMed electronic databases. Only studies using a post-chemoradiotherapy PET for nodal residual disease evaluation were included in the present review. Both prospective and retrospective studies were included. Information regarding sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET for detecting nodal residual disease after definitive chemoradiotherapy for HNSCC was extracted and analyzed.

Results—Twenty published studies were included in the present review. Existing data suggest that a negative post-chemoradiotherapy PET scan is associated with a negative predictive value up to 100%. The sensitivity of PET in detecting nodal residual disease is greater for scans performed 10 weeks after definitive treatment with chemoradiotherapy for HNSCC.

Conclusions—Further studies are needed to quantify the reliability of PET in detecting nodal residual disease after chemoradiotherapy for locoregionally advanced HNSCC. The optimal timing of PET imaging after chemoradiotherapy remains to be defined.

Keywords

Positron Emission Tomography; Neck Dissection; Head and Neck Cancer

INTRODUCTION

Positron Emission Tomography (PET) is a functional imaging study that has been increasingly used for staging, treatment planning, and post-treatment surveillance of malignant tumors including head and neck squamous cell carcinoma (HNSCC) [1, 2]. The most commonly used positron-emitting tracer in oncology is the glucose analog [18F] fluorodeoxyglucose (FDG), which accumulates in a wide variety of tumors due to the increased cellular metabolic demand and glucose avidity of cancer cells compared to most

normal human tissues. Malignant cells take up and entrap the radiolabelled glucose, which is not metabolized further and acts as a positron-emitting tracer [2–4].

The purpose of the current clinical review is to describe the role of PET for assessment of residual neck disease following definitive chemoradiotherapy for HNSCC.

NECK DISSECTION AFTER CONCURRENT CHEMORADIO THERAPY FOR LOCOREGIONALLY ADVANCED HNSCC

The role of neck dissection after definitive chemoradiotherapy for patients with high volume cervical nodal disease at the time of HNSCC diagnosis remains controversial [5, 6]. Studies performed prior to the chemoradiotherapy era demonstrated superior results for patients with advanced nodal disease (N2) treated with radiotherapy followed by a neck dissection for patients with HNSCC as compared to patients treated with radiation therapy alone [7, 8]. Based on these results, planned neck dissections are routinely performed at some cancer centers, irrespective of clinical or radiological response to the chemoradiotherapy in patients with HNSCC with extensive neck disease (N2 and N3) at presentation [5].

There is a growing body of evidence to indicate that modern chemoradiotherapy regimens provide an increased locoregional control for patients with HNSCC, thus leading to a debate regarding the need for a planned neck dissection after chemoradiotherapy [9, 10]. Furthermore, although a planned neck dissection reduces the incidence of neck recurrences, it is unclear if a neck dissection significantly improves disease free survival or overall survival for patients with locoregionally advanced HNSCC treated with definitive chemoradiotherapy [11–13]. Given the high rate of complications following post-radiotherapy neck dissections, the procedure may be avoided in unnecessary cases, while reserved for selected patients with nodal residual disease [14–17]. Moreover, recent data have demonstrated that a selective neck dissection performed in cases of persistent or recurrent disease is associated with an equivalent clinical outcome, but with less morbidity when compared with a more extensive neck dissection procedure [18].

MICROSCOPIC RESIDUAL DISEASE AFTER DEFINITIVE CHEMORADIO THERAPY FOR LOCOREGIONALLY ADVANCED HNSCC

A significant percentage of patients with a clinical complete response following definitive chemoradiotherapy treatment for locoregionally advanced HNSCC may harbor occult nodal residual metastases. The principle of a planned neck dissection is based on the assumption that this nodal residual disease will inevitably develop into neck recurrences. However, the simple presence of post-chemoradiotherapy residual tumor cells in the cervical nodal chain does not always correlate with future risk for a nodal failure [19]. Microscopic residual disease rates as high as 35% were documented in a review by Stenson *et al.* in patients with locoregionally advanced HNSCC after definitive concurrent chemoradiotherapy (50% of patients with N3 nodal disease and 36% of patients with N2 disease) [20]. Despite these findings, the actual rate of neck recurrences for patients with a clinically complete response after definitive chemoradiotherapy without a neck dissection was significantly lower than the reported rate of microscopic residual disease in the neck dissection specimens [20, 11]. Pellitteri *et al.* demonstrated that a higher incidence of residual viable cells was found in series in which the neck dissection was performed early after completion of chemoradiotherapy. Furthermore, they recommended the evaluation of the response to definitive chemoradiotherapy to be performed > 12 following completion of treatment [5]. Taken together, these findings suggest that a planned neck dissection may be delayed or avoided in a subgroup of locoregionally advanced HNSCC patients with clinically negative

necks following definitive chemoradiotherapy. However, the clinical parameters that reliably predict a complete pathological response in these patients remain undefined.

NECK EVALUATION AFTER DEFINITIVE CHEMORADIO THERAPY FOR LOCOREGIONALLY ADVANCED HNSCC

Clinical complete response of nodal disease following definitive chemoradiotherapy for HNSCC is difficult to assess. Post-treatment physical examination of the neck is limited due to post-radiation changes of the skin and subcutaneous soft tissues and the muscles of the neck [5]. The role of computed tomography (CT) for identifying the residual cervical metastases in this group of cancer patients is controversial.

Velazquez *et al.* analyzed the neck dissection specimens in patients with locally advanced head and neck cancer treated with definitive chemoradiotherapy who achieved a clinical complete response and underwent post-treatment planned neck dissection [21]. The radiological post-treatment nodal residual disease was defined as the presence of cervical lymph nodes larger than 1 cm diameter, multiple lymph nodes, or confluent lymph nodes larger than 0.8 cm diameter, the presence of nodal central necrosis, and extracapsular extension. The reported sensitivity of CT scan was 85% with a specificity of only 24%. The positive predictive and negative predictive values were 40% and 73%, respectively [21]. The authors concluded that the use of CT scans as the only indicator for determining the need for neck dissection after definitive radiotherapy/chemoradiotherapy for locoregionally advanced HNSCC patients was inadequate [21]. However, Liauw *et al.* correlated post-radiation neck response on CT scan with the pathological response on neck dissection specimens and found a negative predictive value for pathological nodal residual disease of 94% for the radiological complete response. They defined clinically complete response as the absence of any lymph node larger than 1.5 cm diameter and absence of focally abnormal cervical lymph nodes on a contrast-enhanced CT performed one month after completion of radiotherapy [22]. Nonetheless, Ojiri *et al.* showed no significant correlation between post-irradiation lymph node size on CT and pathological results of the neck dissection specimens. No residual tumor cells were pathologically found in 57.4% of patients with lymph nodes larger than 1.5 cm diameter on the CT scan performed after definitive radiotherapy [23]. However, authors also reported that the negative predictive value of post-irradiation CT scans was higher than 95% if lymph nodes were smaller than 1.5 cm and free of any focal defect (low-attenuation or calcification) and without radiologic extracapsular spread [23].

Positron Emission Tomography-Computed Tomography (PET-CT) integrates the functional PET imaging with the anatomical CT data to allow a precise anatomic localization of hypermetabolic areas [24]. PET-CT was shown to be more accurate in the pre- and post-treatment setting than PET or CT alone for HNSCC detection and anatomic localization [24–26]. Andrade *et al.* showed that the accuracy of PET-CT to detect residual disease after definitive chemoradiotherapy of 85.7% was higher when compared with 67.9% for contrast-enhanced CT scan. The overall specificity of CT scan for detecting residual or recurrent disease was only 46.7%, and further decreased to 28% if the imaging study was performed after 8 weeks from the end of radiation. Conversely, the overall specificity for detecting residual or recurrent disease on PET-CT was 93.3%, and increased to 100% if the imaging study was performed after 8 weeks from the end of radiation [26].

PET FOR NECK EVALUATION AFTER DEFINITIVE CHEMORADIO THERAPY FOR LOCOREGIONALLY ADVANCED HNSCC

Recent data (Table 1) suggest that post-treatment PET imaging appears to be a promising tool for evaluating residual nodal disease and determining the necessity of a neck dissection

in patients with locoregionally advanced HNSCC who achieve a complete clinical and radiological response after definitive chemoradiotherapy [27–39].

The timing for post-treatment PET imaging may influence the accuracy of this imaging study for the neck evaluation following chemoradiotherapy and remains to be defined [31]. PET scans performed too early after chemoradiotherapy have increased false positive and false negative rates. Ryan *et al.* demonstrated that when PET scan is performed more than 1 month after the end of radiation the sensitivity and negative predictive value increase to 100%, compared to 44% and 84%, respectively for the same imaging study performed within 1 month following the completion of the treatment [36]. Yao *et al.* demonstrated that neck dissection can be safely avoided for the subset of patients with locoregionally advanced HNSCC (N2 disease) who achieve a clinical complete response after definitive radiotherapy and have a negative PET scan performed 12 weeks following completion of treatment. This approach was safe even for patients with clinically small residual disease if the post-treatment PET scan was negative [27, 29]. The negative predictive value of the PET scan was 100% in this study [29].

Similar data (Table 2) has been published by using PET-CT for excluding residual locoregional disease after definitive chemoradiotherapy for HNSCC [40–45]. Ong *et al.* showed that the sensitivity and specificity are higher if the PET-CT study is performed after 12 weeks or more from the end of chemoradiotherapy. However, the negative predictive value remained high regardless if the study was performed before or after 12 weeks from the end of treatment [41]. Nayak *et al.* reported post-chemoradiotherapy PET-CT sensitivity of 87.5% and specificity of 91% to detect nodal residual disease for patients with locoregionally advanced HNSCC undergoing post-treatment surveillance scans using PET-CT [40]. The first post-chemoradiotherapy PET-CT was performed between 2 to 6 months and then every 3 to 4 months. The negative predictive value after chemoradiotherapy was 97% for patients with locoregionally advanced HNSCC. Neck dissections were avoided in 85% of patients who had no evidence of regional neck disease after a median follow up of 18 months [40].

Other studies demonstrated that the addition of post-treatment PET scans did not improve the positive and negative predictive values of CT scan or regular clinical exams for nodal residual disease after definitive chemoradiotherapy in locoregionally advanced HNSCC. Nonetheless, negative PET scan results in this setting were highly predictive for the nodal disease control [41]. McCollum *et al.* showed that the sensitivity and specificity of PET after induction chemotherapy followed by concurrent chemoradiotherapy were 67% and 53%, respectively, for detecting nodal occult residual disease in patients with locoregionally advanced HNSCC [31]. The reported overall accuracy of PET for post-chemoradiotherapy neck evaluation in this study was only 58%, with a negative predictive value of 73%. These modest results of PET for post-treatment neck evaluation may be related to the lack of pre-treatment baseline PET imaging for comparison and the early use of PET shortly after completion of chemoradiotherapy. Several patients in this cohort underwent the post-treatment PET scan in as little as 4 weeks from the end of chemoradiotherapy [31]. A delayed period of time for obtaining post-treatment PET scans may have improved the accuracy of this imaging modality for the neck evaluation. Gourin *et al.* reported data on patients with locoregionally advanced HNSCC (N2 neck disease) who achieved a clinical complete response after chemoradiotherapy and had a PET-CT performed 8 to 11 weeks after the end of treatment showing no distant metastases. All patients in this study underwent a planned modified radical neck dissection, and pathologic nodal residual disease was confirmed in only 31% of the patients [42]. The sensitivity and specificity of PET-CT in detecting the nodal residual disease after chemoradiotherapy in this group of patients were 60% and 36%, respectively. The low sensitivity and specificity of PET-CT in detecting

residual neck disease after chemoradiotherapy in this study may be explained by the short interval between the end of treatment and PET-CT scan [42]. Moreover, recent data published by Moeller *et al.* suggested that PET-CT may be the imaging modality of choice for assessment of treatment response in selected head and neck cancer patients with high-risk disease, particularly those with Human Papillomavirus (HPV)-negative tumors [43]. Ninety-eight patients with loco-regionally advanced carcinoma of the oropharynx, hypopharynx and larynx were prospectively enrolled and treated with definitive radiotherapy/chemoradiotherapy. A PET-CT and contrast-enhanced CT imaging studies were performed 8 weeks after completion of treatment. Functional and anatomical imaging response was significantly correlated with clinical and pathological response. The positive and negative predictive values of PET-CT scanning were similar to those of contrast-enhanced CT-alone in the unselected study population. However, PET-CT outperformed contrast-enhanced CT-alone for patients at high-risk of treatment failure: those with HPV-negative disease, history of tobacco use, and non-oropharyngeal primary sites [43].

Figure 1 represents reported negative predictive values (NPV) of FDG-PET for detecting nodal residual disease following chemoradiotherapy for locally-advanced head and neck cancer in the studies discussed above.

Moreover, the pooled sensitivity, specificity, positive predictive value and negative predictive value of PET for detecting residual disease or recurrence of HNSCC were 94%, 82%, 75% and 95%, respectively in a recent systematic review and meta-analysis [47]. The sensitivity was greater when the PET scan was performed 10 weeks or longer after the end of definitive radiotherapy or chemoradiotherapy [47]. These findings suggest that PET scan is highly predictive for nodal complete response following chemoradiotherapy and advocate the use of PET as a prevailing tool for neck evaluation following chemoradiotherapy for locoregionally advanced HNSCC [47].

CONCLUSIONS

Existing data suggest that a negative PET scan performed 10 weeks or longer after treatment is associated with a high negative predictive value and can be used to guide additional treatments for patients with locally advanced HNSCC treated with definitive chemoradiotherapy. With a negative predictive value of more than 95% reported in several recent studies, a negative PET or PET-CT performed following chemoradiotherapy appears to be a reliable predictor of pathologically-negative nodal residual disease for locoregionally advanced HNSCC patients [48] and should be further evaluated prospectively.

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Fig. 1. Reported negative predictive value of Positron Emission Tomography (PET) for detecting residual neck disease following chemoradiotherapy for locally-advanced head and neck cancer. NPV is plotted against the approximate interval from completion of chemoradiotherapy to PET imaging. Median time intervals were used whenever available. In other cases, timing was approximated based on available information (eg: “8 to 11 weeks” was approximated as 9.5 weeks). Larger circles indicate greater sample size.

Positron Emission Tomography (PET) for Neck Evaluation after Chemoradiotherapy in Patients with Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

Table 1

Study	Number of Patients	Time from RT Completion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Yao <i>et al.</i> [27]	53	12 weeks	100	94	43	100	-
Yao <i>et al.</i> [28]	85	3–6 months	100	98	78	100	
Yao <i>et al.</i> [29]	41	12–16 weeks	-	-	80	100	-
Tan <i>et al.</i> [30]	48	8–12 weeks	25	83	15	90	76
McCollum <i>et al.</i> [31]	40	4–12 weeks	67	53	46	73	58
Kitagawa <i>et al.</i> [32]	23	> 4 weeks	-	73.9	-	-	-
Hanasono <i>et al.</i> [33]	84	within 12 weeks	86	73	-	-	-
Goguen <i>et al.</i> [34]	28	-	-	-	-	75	-
Brkovich <i>et al.</i> [35]	19	8–12 weeks	75	64.7	33	91.7	-
Ryan <i>et al.</i> [36]	103	>1 month < 1 month	100 44			100 84	
Yao <i>et al.</i> [37]	188	within 12 months	86	97	71	99	
Porecdu <i>et al.</i> [38]	39	median 12 weeks (range 8–32 weeks)	83	93	71	97	
Porecdu <i>et al.</i> [39]	112	12			77.8	98.1	

RT, radiotherapy; PPV, positive predictive value; NPV, negative predictive value.

Table 2

Positron Emission Tomography-Computerized Tomography (PET-CT) for Neck Evaluation after Chemoradiotherapy in Patients with Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

Study	Number of Patients	Time from RT Completion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Nayak <i>et al.</i> [40]	43	between 2–6 months	88	91	70	97	91
Ong <i>et al.</i> [41]	65	8 weeks	71	89	38	97	88
Gourin <i>et al.</i> [42]	32	between 8–11 weeks (SUV > 3.0)	60 40	36 91	30 67	67 77	-
Moeller <i>et al.</i> [43]	98	8 weeks	75	76.1	27.3	96.2	-
Gupta <i>et al.</i> [44]	15	8–10 weeks	62.5	98	83.3	94.1	93
Rabalais <i>et al.</i> [45]	52	median 11.8 weeks (range 3.7–29.4)	100	87.5	40	100	88
Gourin <i>et al.</i> [46]	17	8–10 weeks (SUV > 3.0)	40 23	25 83.3	18.2 33.3	50 71.4	

RT, radiotherapy; PPV, positive predictive value; NPV, negative predictive value