

FDG-PET/CT in the Assessment of Treatment Response after Oncologic Treatment of Head and Neck Squamous Cell Carcinoma

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ABSTRACT

BACKGROUND: In many centers, ¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) is used to monitor treatment response after definitive (chemo)radiotherapy [(C)RT] for head and neck squamous cell carcinoma (HNSCC), but its usefulness remains somewhat controversial. We aimed at assessing the accuracy of FDG-PET/CT in detecting residual disease after (C)RT.

METHOD: All HNSCC patients with FDG-PET/CT performed to assess treatment response 10–18 weeks after definitive (C)RT at our institution during 2008–2010 were included. The patient charts were reviewed for FDG-PET/CT findings, histopathologic findings, and follow-up data. The median follow-up time for FDG-PET/CT negative patients was 26 months.

RESULTS: Eighty-eight eligible patients were identified. The stage distribution was as follows: I, $n = 1$; II, $n = 15$; III, $n = 17$; IV, $n = 55$. The negative predictive value, positive predictive value, specificity, sensitivity, and accuracy of FDG-PET/CT in detecting residual disease were 87%, 81%, 94%, 65%, and 85%, respectively. The corresponding specific figures for the primary tumor site were 91%, 71%, 94%, 59%, and 86% and for the neck 93%, 100%, 100%, 75%, and 94%, respectively.

CONCLUSIONS: In patients who have received definitive (C)RT for HNSCC, post-treatment FDG-PET/CT has good potential to guide clinical decision-making. Patients with negative scan can safely be followed up clinically only, while positive scan necessitates tissue biopsies or a neck dissection to rule out residual disease.

KEYWORDS: FDG-PET/CT, head and neck squamous cell carcinoma, HNSCC, chemoradiotherapy, response assessment

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This paper was subject to independent, expert peer review by a minimum of two blind peer reviewers. All editorial decisions were made by the independent academic editor. All authors have provided signed confirmation of their compliance with ethical and legal obligations including (but not limited to) use of any copyrighted material, compliance with ICMJE authorship and competing interests disclosure guidelines and, where applicable, compliance with legal and ethical guidelines on human and animal research participants. The preliminary results of this study were presented at the 5th European Conference on Head and Neck Oncology, Poznan, Poland, April 18–21, 2012.

Background

In the current treatment protocols, organ-preserving oncologic treatment is often advocated for patients with newly diagnosed head and neck squamous cell carcinoma (HNSCC) with surgery as a salvage option. After oncologic treatment, ie radiotherapy or chemoradiotherapy [(C)RT], accurate assessment of treatment response is essential. Early detection of residual disease is of utmost importance to recognize patients

who will need salvage surgery. On the other hand, patients with complete response need to be identified to avoid unnecessary surgical or endoscopic procedures including tissue biopsies, which may carry an increased risk of complications in this patient group treated with (C)RT.¹

Anatomical distortion caused by the tumor and therapy-induced changes in tissues make the evaluation of treatment response challenging for conventional anatomical



imaging methods [computed tomography (CT), MRI], and thus, their accuracy in this setting has not been optimal.^{2,3} ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging, and recently, FDG-PET/CT imaging have been recommended for assessing treatment response after oncologic treatment of HNSCC. The diagnostic accuracy of FDG-PET or FDG-PET/CT is reportedly good in this setting. Particularly, the negative predictive value (NPV) has been reported to be high. In two recent meta-analyses, the NPV was around 95% for both primary site and neck, provided that FDG-PET/CT was not performed earlier than 10–12 weeks after completion of (C)RT.^{4,5}

According to the present guidelines at our institution, FDG-PET/CT is performed 12 weeks after completion of definitive (C)RT to assess treatment response. Patients with negative FDG-PET/CT and with no clinical suspicion of residual disease are regarded as having complete response and are only followed up clinically. In cases with suspected residual disease in FDG-PET/CT and/or clinically, biopsies and/or salvage surgery is considered. To audit this FDG-PET/CT based protocol, we retrospectively analyzed the accuracy of FDG-PET/CT imaging in the assessment of treatment response after definitive (C)RT for HNSCC.

Patients and Methods

Institutional approval to conduct this retrospective study was obtained. We included all patients with FDG-PET/CT performed to assess treatment response after definitive (C)RT for previously untreated HNSCC at our institution during 2008–2010. The hospital records were reviewed and data on patient characteristics, treatment, FDG-PET/CT findings, histopathology, and follow-up were collected. Patients with FDG-PET/CT performed earlier than 10 weeks or later than 18 weeks after completion of (C)RT were excluded. For patients with negative FDG-PET/CT scan and no proven recurrence (ie patients with FDG-PET/CT considered true negative), the follow-up time was calculated from the completion of (C)RT to the date of last visit or to the death. The study period was chosen to ensure a sufficient sample size and an adequate follow-up time for the analysis. The diagnostic accuracy [NPV, positive predictive value (PPV), specificity, sensitivity, and accuracy] of FDG-PET/CT in detecting residual tumor was calculated generally and specifically for the primary site and neck. Histopathologic and clinical follow-up data served as the standard reference. When assessing the neck, only patients diagnosed with clinically N+ disease were taken into account. Post-treatment histopathologic data as a reference standard were available for all patients who had had positive FDG-PET/CT or clinical suspicion of residual disease indicating a neck dissection and/or biopsies from the primary tumor area. Patients with negative FDG-PET/CT and with no clinical suspicion of residual disease had only been followed up clinically, and they had follow-up data with possible later imaging and histopathology as a reference standard.

Oncologic Treatment

Of the 88 eligible patients, 12 (14%) were treated by radiotherapy only and 76 (86%) by (C)RT. Intensity modulated radiotherapy (IMRT) was used in 85 patients (97%), and three patients (3%) were treated by conventional 3-D radiotherapy.

In the patients treated by IMRT, the clinical target volume (CTV1) typically first included the gross tumor volume (GTV) with 1 cm margins and the elective nodal areas. A 3–5 mm margin was added to CTV1 to obtain the planning target volume (PTV1). This volume was irradiated to a cumulative dose of 50 Gy in 2 Gy daily fractions in five weeks. The primary tumor area and areas with nodal metastasis (PTV2-3) were then irradiated up to a mean total dose of 69 Gy (range 58–72 Gy). Three patients with T2 laryngeal cancer were treated by conventional 3-D radiotherapy from wedged lateral laryngeal fields. The mean total treatment time was 51 days (range 37–84 days).

Most of the patients ($n = 63$, 72%) treated by (C)RT were scheduled to receive cisplatin 40 mg/m² weekly up to six cycles during the radiotherapy. Eight patients (9%) received weekly cetuximab during the radiotherapy course. Two patients with nasopharyngeal cancer were treated with cisplatin 100 mg/m² at three-week intervals up to three times concurrently with radiotherapy. Weekly carboplatin, cisplatin together with panitumumab, and cisplatin combined with etoposide were used each in one patient.

FDG-PET/CT Imaging Method

The patients were instructed to fast for six hours before the imaging. Blood glucose level was measured, and if it was <10 mmol/L, the study was performed. After an intravenous injection of approximately 350–450 MBq (5 MBq/kg) of ¹⁸F-FDG, the patients rested for 60 minutes in a quiet, dimly lit room. Images were acquired with a Gemini PET/CT scanner (Philips, USA). After conducting a CT survey (120 kV, 30 mAs), the imaging was started applying a head and neck protocol. Body images were obtained first, followed by head and neck images. The body imaging was conducted from clavicle to midthigh, with arms raised above shoulder level. CT (120–140 kV, 50–60 mAs, a section width of 4 mm) was applied first followed by PET (8 cm bed position, 1.5 minutes per frame). During the head and neck images, the patients' arms were positioned down, and the head was stabilized with a head rack; CT (120 KeV, 50 mAs, a section width of 3 mm) was again applied first, followed by PET (8 cm bed position, 2.5 minutes per frame). Focal uptake distinguishable from the background, which could not be considered physiologic, reactive, or inflammatory, was interpreted to be pathological uptake. No predetermined standardized uptake value (SUV) threshold was used in the analysis. A nuclear physician and a radiologist examined the PET/CT images together, and the nuclear physician made the final interpretation. In this study, the results are based on the original interpretations. In the analysis, a scan with no pathological focal FDG-accumulation



was considered negative even in the presence of residual anatomical changes in the CT portion of the imaging.

Results

The patient characteristics of the 88 eligible patients are presented in Table 1. FDG-PET/CT was performed at a median of 13 weeks post (C)RT (range 10–18 weeks). The median follow-up time of patients with negative FDG-PET/CT and no proven recurrence was 26 months (range 5–55 months).

FDG-PET/CT was negative for residual disease in 67 (76%) patients. In nine (13%) out of these 67 patients, residual disease or recurrent disease was confirmed during further follow-up. FDG-PET/CT was positive indicating residual disease in 21 (24%) patients. In 17 (81%) out of these 21 patients, residual disease was confirmed (Table 2). Accordingly, the overall NPV, PPV, specificity, sensitivity, and accuracy of FDG-PET/CT in detecting residual disease were 87%, 81%, 94%, 65%, and 85%, respectively (Table 3). The corresponding figures specifically for the primary site and the neck nodes are presented in Tables 2 and 3.

Table 1. Patient characteristics.

	n (%)
Sex	
Male	69 (78)
Female	19 (22)
Tumour site	
Oral cavity	1 (1)
Nasopharynx	4 (5)
Oropharynx	39 (44)
Hypopharynx	20 (23)
Larynx	24 (27)
T classification	
T1	11 (13)
T2	28 (32)
T3	26 (30)
T4	23 (26)
N classification	
N0	34 (39)
N1	7 (8)
N2	47 (53)
N3	0 (0)
Stage	
I	1 (1)
II	15 (17)
III	17 (19)
IV	55 (63)
Treatment	
Radiotherapy	12 (14)
Chemoradiotherapy	76 (86)

Table 2. True and false positive and negative findings.

	RESIDUAL DISEASE	PET-CT	
		POSITIVE	NEGATIVE
Overall (n = 88)	Yes	17	9
	No	4	58
Primary tumour (n = 88)	Yes	10	7
	No	4	67
Neck (n = 54)*	Yes	9	3
	No	0	42

Note: *Only patients diagnosed with N+ disease.

Distant metastases were detected in three (3%) patients who all had persistent disease also locoregionally.

In addition to the FDG-PET/CT findings related to the index tumor, other previously unknown malignant tumors were detected in two patients: a second primary esophageal carcinoma in one patient and a pulmonary metastasis of previously treated adenocystic carcinoma of lip in one patient. The esophageal tumor was treated with curative intent, and there has been no recurrence during the follow-up.

Discussion

The aim of this study was to audit our current FDG-PET/CT based approach to assess treatment response after definitive (C)RT for patients with newly diagnosed HNSCC. The present results of a series of 88 patients are in line with previously reported data and further confirm the reasonably good accuracy of FDG-PET/CT in this setting. The value of a negative FDG-PET/CT was particularly highlighted in the present study, with the overall NPV being 87%. When analyzed separately for the primary site and neck, the NPV was 91% and 93%, respectively. These figures are well in line with two systematic reviews assessing the diagnostic accuracy of FDG-PET or FDG-PET/CT, in both of which the pooled NPV of FDG-PET/CT for both primary site and neck was 95%.^{4,5} Therefore, it seems feasible to rely on a negative FDG-PET/CT result in the clinical follow-up of this patient population.

False positive FDG-PET/CT findings do occur, and in the aforementioned review articles, the pooled PPV figures were 75% and 59% for the primary site and 49% and 52% for the neck.^{4,5} We recorded better PPV figures, the overall PPV being 81%, and when analyzed separately for primary site and neck, the figures were 71% and 100%, respectively. All the false positive findings occurred at the primary site, and thus, we did not have a single case in which FDG-PET/CT would have falsely indicated residual disease in the neck. On the other hand, the sensitivity in our study remained somewhat low being 65% in general, and 59% and 75% for the primary site and neck, respectively, which is lower than in most other studies. Hence, a question arose whether some focal ¹⁸F-FDG accumulations representing residual tumor had been interpreted as inflamma-

**Table 3.** Ability of FDG-PET/CT to detect residual disease.

	OVERALL (%)	PRIMARY (%)	NECK (%)
NPV	87	91	93
PPV	81	71	100
Specificity	94	94	100
Sensitivity	65	59	75
Accuracy	85	86	94

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

tory lesions when assessing the neck nodes. Therefore, the false negative findings in the neck nodes were re-assessed, and it was found that in one out of three such cases, different interpretation of the images would have been justifiable in a retrospective analysis.

It has been shown that optimal timing of FDG-PET/CT imaging, ie not earlier than 10–12 weeks after completion of (C)RT, is crucial to assure good accuracy.^{4,5} When performed earlier, accumulation of ¹⁸F-FDG may reflect treatment-induced inflammatory changes in tissues instead of residual disease. On the other hand, small traces of residual tumor may not be detected in FDG-PET/CT soon after treatment, but will become detectable a few weeks later. This conflicts the need for prompt diagnostics and salvage treatment of patients with residual disease. It has been suggested that early surgical salvage will result in improved locoregional control and survival rates.⁶ In addition, delay in performing salvage surgery may increase the risk of surgical complications. It has been proposed that there is a therapeutic window for salvage surgery at approximately six weeks after cessation of (C)RT.⁷ At this time point, treatment-induced acute tissue toxicity will be mostly healed, but the late toxicity will not yet be developed. The drawback of using FDG-PET/CT in monitoring treatment response at 12 weeks post-treatment is that the option for the suggested therapeutic window at 6 weeks will be lost. However, there are no means available for accurate assessment of treatment response at an earlier time point. Despite this, it has been suggested that planned neck dissections performed a few weeks after (C)RT for patients with N2–N3 neck disease are no longer justified, because the probability of isolated neck recurrence following a complete response is very low.^{8,9} Even the excision of residual lymphadenopathy without FDG avidity has been questioned because of very low risk of viable tumor cells.^{10,11} In the current series, one patient without clinical suspicion of residual disease had persistent anatomical changes in the neck nodes in the CT portion of the imaging with no FDG avidity. A selective neck dissection was performed and no viable tumor tissue was detected in the histopathological examination. In the case of clinically evident residual neck mass after (C)RT, it is our policy to remove the residual tumor for histopathological analysis before the scheduled FDG-PET/CT imaging.

The use of pre-treatment FDG-PET/CT is advocated by many centers.^{11–13} FDG-PET/CT has been shown to effectively diagnose second primary tumors and distant metastasis in HNSCC patients.^{12–16} Pre-treatment FDG-PET/CT also allows more targeted endoscopies and biopsies instead of pan-endoscopies in search for unknown or second primary tumors. Correct staging of patients with distant metastasis is fundamental for optimal treatment planning. In addition, a baseline FDG-PET/CT is useful as a reference standard when assessing the post-treatment images for treatment response.¹¹ Furthermore, pre-treatment FDG-PET/CT images can be used in radiotherapy target delineation.¹⁷

According to our institutional guidelines, the response assessment FDG-PET/CT should be performed at 12 weeks after cessation of the (C)RT. However, in the present retrospective analysis we found large variation in the timing of imaging, with the median interval still being approximately 13 weeks. As discussed previously, FDG-PET/CT imaging should not be performed earlier than 10–12 weeks after completion of the treatment to assure good accuracy. On the other hand, delayed imaging at a median 16.8 weeks post (C)RT resulted in good accuracy in a study by Prestwich et al.¹¹ The correct timing of FDG-PET/CT was not in the focus of our analysis, and we thus chose to include all patients imaged 10–18 weeks post (C)RT.

In some cases, distant metastases may develop soon after completion of (C)RT although not detected during initial diagnostic workup. For clinical decision making, diagnosing distant spread of the disease at this phase is critical because radical surgery for locoregional residual disease will probably not be considered beneficial in these cases. FDG-PET/CT imaging is recognized as a preferred method for the detection of distant metastases in HNSCC,^{13,15,16} which further supports its use also in monitoring treatment response after (C)RT. In the present series, three patients (3%) were found to have distant metastasis in the post-treatment FDG-PET/CT, and one patient was found to have pulmonary metastases of a previous cancer.

The current study is limited mainly by the size of the patient series and by the retrospective nature of the analysis. It must be noted, however, that in the two meta-analyses cited earlier, there are only a few studies with a larger patient cohort. The present heterogeneity in the treatment modalities and in the patient characteristics reflect the typical clinical practice in the management of head and neck cancer. The aim of the present study was to retrospectively audit our current protocol, and we did not address the question about the best available imaging modality in the post-treatment setting. To further clarify this issue, new prospective, comparative studies will be needed including also financial aspects.

In conclusion, the diagnostic accuracy of FDG-PET/CT in the assessment of treatment response after definitive (C)RT for HNSCC was good, further supporting its use in this setting. The NPV, specificity, and accuracy were high for both



primary site and neck. Also the PPV for the neck was high: there were no false positive findings in the assessment of neck nodes. Post-treatment FDG-PET/CT obviously has potential to guide clinical decision-making. Patients with negative scan can fairly safely be followed up clinically only, while positive scan necessitates a neck dissection and/or biopsies from the primary tumor area to rule out or confirm residual tumor.

Author Contributions

HK was involved in the study design, collection and statistical analysis of data, and drafting of the manuscript. TM, JS, and KS were involved in the study design, collection of data, and drafting of the manuscript. AM was involved in the study design and in drafting and revisions of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Sewnaik A, Keereweer S, Al-Mamgani A, et al. High complication risk of salvage surgery after chemoradiation failures. *Acta Otolaryngol.* 2012;132(1):96–100.
2. Kubota K, Yokoyama J, Yamaguchi K, et al. FDG-PET delayed imaging for the detection of head and neck cancer recurrence after radio-chemotherapy: comparison with MRI/CT. *Eur J Nucl Med Mol Imaging.* 2004;31(4):590–595.
3. Lell M, Baum U, Greess H, et al. Head and neck tumors: imaging recurrent tumor and post-therapeutic changes with CT and MRI. *Eur J Radiol.* 2000;33(3):239–247.
4. Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol.* 2008;33(3):210–222.
5. Gupta T, Master Z, Kannan S, et al. Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* 2011;38(11):2083–2095.
6. Yom SS, Machtay M, Biel MA, et al. Survival impact of planned restaging and early surgical salvage following definitive chemoradiation for locally advanced squamous cell carcinomas of the oropharynx and hypopharynx. *Am J Clin Oncol.* 2005;28(4):385–392.
7. Lango MN, Myers JN, Garden AS. Controversies in surgical management of the node-positive neck after chemoradiation. *Semin Radiat Oncol.* 2009;19(1):24–28.
8. Karakaya E, Yetmen O, Oksuz DC, et al. Outcomes following chemoradiotherapy for N3 head and neck squamous cell carcinoma without a planned neck dissection. *Oral Oncol.* 2013;49(1):55–59.
9. Hamoir M, Ferlito A, Schmitz S, et al. The role of neck dissection in the setting of chemoradiation therapy for head and neck squamous cell carcinoma with advanced neck disease. *Oral Oncol.* 2012;48(3):203–210.
10. Ong SC, Schöder H, Lee NY, et al. Clinical utility of 18F-FDG PET/CT in assessing the neck after concurrent chemoradiotherapy for locoregional advanced head and neck cancer. *J Nucl Med.* 2008;49(4):532–540.
11. Prestwich RJ, Sykes J, Carey B, Sen M, Dyker KE, Scarsbrook AF. Improving target definition for head and neck radiotherapy: a place for magnetic resonance imaging and 18-fluoride fluorodeoxyglucose positron emission tomography? *Clin Oncol (R Coll Radiol).* 2012;24(8):577–589.
12. Strobel K, Haerle SK, Stoeckli SJ, et al. Head and neck squamous cell carcinoma (HNSCC)—detection of synchronous primaries with (18)F-FDG-PET/CT. *Eur J Nucl Med Mol Imaging.* 2009;36(6):919–927.
13. Gourin CG, Watts T, Williams HT, Patel VS, Bilodeau PA, Coleman TA. Identification of distant metastases with PET-CT in patients with suspected recurrent head and neck cancer. *Laryngoscope.* 2009;119(4):703–706.
14. Haerle SK, Schmid DT, Ahmad N, Hany TF, Stoeckli SJ. The value of (18)F-FDG PET/CT for the detection of distant metastases in high-risk patients with head and neck squamous cell carcinoma. *Oral Oncol.* 2011;47(7):653–659.
15. Senft A, de Bree R, Hoekstra OS, et al. Screening for distant metastases in head and neck cancer patients by chest CT or whole body FDG-PET: a prospective multicenter trial. *Radiother Oncol.* 2008;87(2):221–229.
16. Uyl-de Groot CA, Senft A, de Bree R, Leemans CR, Hoekstra OS. Chest CT and whole-body 18F-FDG PET are cost-effective in screening for distant metastases in head and neck cancer patients. *J Nucl Med.* 2010;51(2):176–182.
17. Delouya G, Igidbashian L, Houle A, et al. ¹⁸F-FDG-PET imaging in radiotherapy tumor volume delineation in treatment of head and neck cancer. *Radiother Oncol.* 2011;101(3):362–368.