RESEARCH ARTICLE

Is FDG –PET-CT A Valuable Tool in Prediction of Persistent Disease in Head and Neck Cancer

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Abstract

Objectives: To evaluate accuracy of FDG-PET CT in prediction of persistent disease in head and neck cancer cases and to determine prognostic value of metabolic tumor response. Materials and Methods: Between 2009 and 2011, 46 patients with squamous cell carcinoma of head and neck receiving PET-CT were treated with definitive radiotherapy, with or without chemotherapy. There were 29 nasopharyngeal, 11 hypopharyngeal, 3 oropharyngeal and 3 laryngeal cancer patients, with a median age of 50.5 years (range 16-84), 32 males and 14 females. All patients were evaluated with PET-CT median 3-5 months (2.4-9.4) after completion of radiotherapy. Results: After a median 20 months of follow up, complete metabolic response was observed in 63% of patients. Suspicious residual uptake was present in 10.9% and residual metabolic uptake in 26.0% of patients. The overall sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET-CT for detection of residual disease was 91% and 81%, 64% and 96% respectively. Two year LRC was 95% in complete responders while it was 34% in non-complete responders. Conclusions: FDG PET CT is a valuable tool for assessment of treatment response, especially in patients at high risk of local recurrence, and also as an indicator of prognosis. Definitely more precise criteria are required for assessment of response, there being no clear cut uptake value indicating residual disease. Futhermore, repair processes of normal tissue may consume glucose which appear as increased uptake in control FDG PET CT.

Keywords: PET-CT - head and neck cancer - nasopharyngeal cancer - response evaluation - SUV

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Introduction

One third of head and neck squamous cell cancer (HNSCC) present with early stage disease amenable to curative surgery or radiotherapy. However remaining two thirds of patients present with locally advanced disease and have a less favorable prognosis (Pfister et al., 1997; Lee et al., 2003; Pignon et al., 2009). Over the recent decades, the management of advanced HNSCC has evolved towards organ preservation and nonsurgical approaches. Concurrent chemoradiotherapy has resulted in substantial gains in loco-regional control and improvement in overall survival (Paccagnella, 1997; Pfister et al., 1997; Lee et al., 2003; Pignon et al., 2009).

Intensity- modulated radiation treatment (IMRT), volumetric arc therapy (VMAT) are relatively new, high conformal radiation techniques with encouraging results in reducing treatment- related side effects, improving loco-regional tumor control, and potentially have a positive impact on the quality of life. Despite these advances, overall complete responses in advanced HNSCC could be as low as 25-35% in specific sites, and complete response rate at the primary site range from 35-55% (Lefebvre et al., 1996; Paccagnella et al., 1997; Lee et al., 2003; Andrade et al., 2006)

Therefore, accurate assessment of treatment response and early detection of tumor recurrence is essential to initiate early salvage therapies. The follow-up and surveillance for head and neck cancer patients have mostly relied on physical examination with short periodic intervals during the first year (every 1 to 3 months). In addition, contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are frequently used. The appearance of edema, scar tissue, and treatment-related tissue changes result repeated endoscopic biopsies to identify persistent or recurrent disease which jeopardizes normal tissue healing in many patients. In addition anatomical complexity of head and neck region makes response evaluation rather difficult, post radiation changes and anatomic distortions after surgery further limit the diagnostic accuracy of these anatomic-based imaging studies in head and neck region (El-Sayed et al., 1996; Rose et al., 1999; Hain et al., 2000; Bastiaannet et al., 2004; DeSantis et al., 2004; Scarfone et al., 2004; Schwartz et al., 2005; Thomas et al., 2005; Yao et al., 2005; Andrade et al., 2006; Higgins et al., 2012).

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The advent of 18-Fluorodeoxyglucose (FDG)- CT has improved clinical staging and treatment evaluation inpatient with HNSCC and nasopharyngeal cancer. Additionally, the early detection of recurrence or residual tumors has improved clinical strategies for treating patients with advanced and incurable HNSCC and nasopharyngeal cancer. The optimal timing of first post treatment PET-CT examination for the detection of recurrences was previously reported to be between 2 and 4 months after therapy (Rose et al., 1999; Hain et al., 2000; Ding et al., 2005; Yao et al., 2005; Andrade et al., 2006).

In this report role of PET-CT accuracy in detection of residual disease is evaluated in our series.

Materials and Methods

Patients

Fourty-six (46) patients with squamous cell head and neck cancer that were treated with definitive Radiotherapy with or without chemotherapy between 2009 and 2011 who had pre- and post- treatment FDG PET-CT imaging were entered in to the study. There were 29 nasopharyngeal, 11 hypopharyngeal, 3 oropharyngeal, 3 laryngeal cancer patients median age being 50.5 years (range 16-84) 32 of them were male, 14 were female. The patient characteristics are summarized in Table 1

Histology was nonkeratinizing nasopharyngeal carcinoma in 29 and squamous cell cancer in 17 patients. One patient has stage I, three had stage II, fourteen had stage III, twenty eight stage IV. Patient characteristics are summarized in Table 1.

Pet CT

All patients were evaluated with FDG PET CT imaging before commencing radiotherapy and median 3.5 months (range 2.4-9.4) after completion of radiotherapy for all patient.

All patients fasted at least 6 hours before injection and their glucose level were under control. PET/CT scan was done 60-75 minutes after intravenous administration of approximately 580 MBq of FDG with thermoplastic mask which is used for radiotherapy planning using an integrated PET/CT scanner which consisted of a full-ring high-resolution LSO PET and a six-slice CT (Siemens Biograph 6; Knoxville, Tennessee, USA). The patients were placed on the scanner table in a supine position and a CT topogram was first acquired to define the axial range of the PET/CT study, covering the area from the skull base to the mid thighs. After that, CT transmission scan with no using i.v. contrast enhancement were acquired with low tube current (130 kVp, 4-76 mAs), a slice thickness of 4.0 mm, 0.6 s gantry rotation, and a collimator width of 6×3 mm. Then, PET emission scanning with duration of 3 min per bed position was performed with the identical transverse field of view in the craniocaudal direction.

Treatment

All patients were treated with radiotherapy most in combination with chemotherapy. Six patients treated with RT alone, fourteen patients received induction chemotherapy and chemoradiotherapy, 25 patients treated with concomitant chemoradiotherapy and one patients received with cetuximab concomitant with RT. Conformal RT was used 13 patients where as 33 patients treated with IMRT. Median dose to primary site and involved nodes 70 Gy (48-70) elective treatment volume received median 50 Gy (45-54). Three patients were treated with Co60 unit and 43 patients were treated with linear accelerators. The patients treatment summarized in Table 2.

Statistical methods

Loco-regional control (lrc) and overall survival (os) were calculated from the date of diagnosis. As event for lrc was defined as any disease progression (local, regional). Survival curves for lrc and os were generated with the method of Kaplan-meier. Cox proportional hazard models were used for univariate analysis (Kaplan and Meier, 1958; Wong et al., 2004). The sensitivity, specificity, positive predictive values(PPV) and negative predictive value(NPV) for tumor detection of FDG PET-CT scans were calculated using the McNemar test. True positive lesion was a lesion seen on FDG PET-CT images and found to be positive for tumor tissue on histological examination or clinical follow up.a false- positive lesion was a lesion seen on FDG PET-CT images but found to be negative for tumor tissue on histological examination or clinical follow up. A true-negative lesion was defined as one that was not seen on FDG-PET CT images and the results of histopatological examination were negative for tumor or clinical follow up was negative. A false-negative lesion was a lesion that was missed on image analysis, but was found to be positive for malignancyon histopatological analysis or clinical follow up. The analyses were performed using SPSS 15.0 software (Kaplan, 1958; Mantel, 1966).

Results

Response to treatment and relationship with loco-regional control and survival

Complete metabolic response was observed in 29 patients, suspicious residual FDG uptake was present in 5 patients and residual FDG uptake was found in 12 patients. After a median follow up 20 months (6.8-36.3), Two years loco-regional control and overall survival rates were 71% and 81% respectively for all patients (Figure 1). Only one local recurrence occurred among complete responders yielding two year loco-regional control rate of 95%, in contrast, patients who found to have suspicious or residual FDG uptake after completion of radiotherapy had two years loco-regional control rate of 34% ($p<0.001$) (Figure 2). The overall sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET-CT for detection of residual disease was 91.7% and 81.3%, 64.7% and 96.3%, respectively.

Metabolic response by tumor site

Among 29 patients with nasopharyngeal carcinoma 24 had complete metabolic response after treatment, of those only one developed local recurrence at 11 months which was treated with re-irradiation and still alive at 17.5 months. Two patients found to have distant metastasis

despite complete metabolic response was achieved at local and regional disease site, both patients were treated with chemotherapy with or without radiotherapy to metastatic sites at liver and pelvic soft tissue. They are still alive 20 and 11 months after diagnosis. Five (5) patients had residual FDG uptake, one of them developed local recurrence at 10 months and treated with re-irradiation. One patient had clinical and metabolic residual disease in the neck which was proved to be negative after excision of lymph node. Three patients had no disease progression on their follow up 19.1, 24.2, 20.1 months respectively.

Only two complete metabolic responce was observed in eleven patients with hypopharyngeal carcinoma. Both patients are alive without evidence of disease for 26 and 34 months respectively. Two patients has minimal so called suspicious residual FDG uptake one of them is still alive without evidence of disease for 25.6 months. Second one developed local recurrence and salvaged with total larynopharyngectomy and esophagectomy. Seven patients had residual FDG uptake on control PET CT, one of them had complete response at primary site but residual disease in the neck who undergone neck dissection immediately after control PET CT. Pathology confirmed tumor cells within involved node he is still alive without evidence of recurrence at 32 months. One patient died of aspiration pneumonia without evidence of local progression at 18 months. One patient is still alive with local disease progression. Four patients died with local and regional uncontrolled disease two of them also developed distant metastasis.

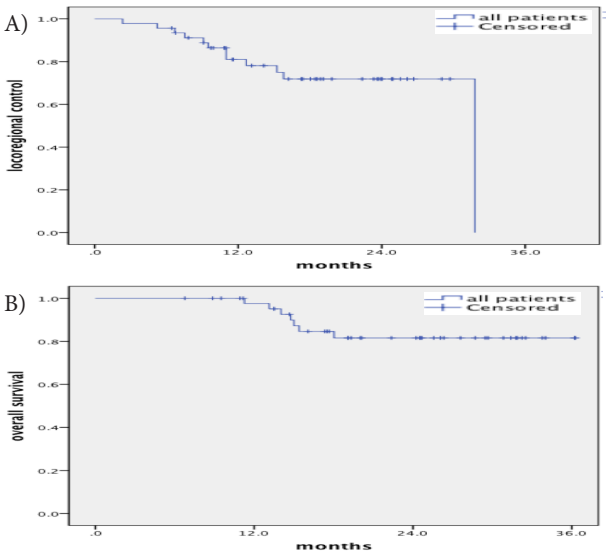

Figure 1. A) Overall Survival of All Patients and B) Locoregional Control of All Patients

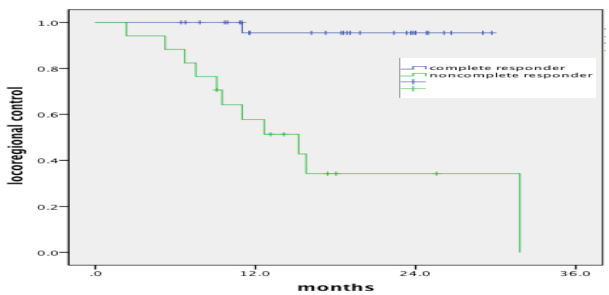

Figure 2. Comparison of Complete Responder and non-Complete Responder

Table 1. Patient Characteristics (n=46) of Patients

Ages, years (range)		50, 5 (16-84)
Sex, male		32 (46)
Follow up (months)		20 (6.8-36.3)
Stage	I	1
	II	3
	III	14
	IV	28
Histology of tumors	SCC	17
	Non-keratinizing NPC	29
Primary sites of tumor	Oropharynx	3
	Larynx	3
	Hypopharynx	11
	Nasopharynx	29

Table 2. Treatment Details of Patients

Induction CT+CTRT	14
Chemoradiotherapy	25
RT+Cetuximab	1
Rt only	6

Table 3. Patterns of Outcome in Patients with Control FDG PET CT Non-Complete Responders

Patients	PET-CT result	Location site	Recurrence	Recurrence site	Follow up (months)
1	suspicious	Nasopharyngeal	absent	-	20.1
2	suspicious	hypopharyngeal	present	Local	19.3
3	suspicious	hypopharyngeal	absent	-	25.6
4	suspicious	oropharyngeal	Present	Regional	14.8
5	suspicious	laryngeal	present	Local	36.3
6	positive	Nasopharyngeal	Absent	-	13.5
7	Positive	Nasopharyngeal	Present	Locoregional	9.5
8	Positive	Nasopharyngeal	Absent	-	19.1
9	Positive	Nasopharyngeal	Absent	-	24.2
10	Positive	hypopharyngeal	Present	Local	13.1
11	Positive	hypopharyngeal	Absent	-	18
12	Positive	hypopharyngeal	Present	Local	14
13	Positive	hypopharyngeal	Present	Locoregional	11.3
14	Positive	hypopharyngeal	Present	Local	8.9
15	Positive	hypopharyngeal	Present	Local	15.4
16	Positive	oropharyngeal	Present	Locoregional	15
17	Positive	hypopharyngeal	Present	regional	31.9

Two out of three patients with oropharyngeal carcinoma had residual metabolic activity in their control PET CT both died with progressive disease 14.8 and 15 months after diagnosis. The other patient had complete metabolic response and alive without evidence of disease at 34.8 months.

Three patients treated for laryngeal carcinoma where evaluated with PET CT two of them had complete response and they are still alive without any progression of disease at 31.4 and 13.5 months respectively. Suspicious metabolic activity was observed in one patient with T4 laryngeal cancer who developed local recurrence at 31.8 months and salvaged with total laryngectomy and still alive at 36.3 months. Out come of patients with non complete response are summarized in Table 3.

Discussion

The role of FDG PET CT imaging has evolved in the management of cancer over the last decade. It is

widely used in detection of primary site in patients with unknown primary tumors, staging of various tumors, target delineation in radiotherapy planning and response evaluation in some tumors. Moreover the mean value of SUV max also demonstrated to be an important prognostic parameter in many tumors (El-Sayed et al., 1996; Rose et al., 1999; Hain et al., 2000; Bastiaannet et al., 2004; DeSantis et al., 2004; Scarfone et al., 2004; Schwartz et al., 2005; Thomas et al., 2005; Yao et al., 2005; Andrade et al., 2006; Higgins et al., 2012). FDG-PET CT imaging has become an important tool in the management of patients with HNC. It is particularly useful in delineating target volumes and can significantly alter volumes defined with CT alone (Schwartz, 2005) and aid in the detection of occult contralateral neck node involvement (Scarfone et al., 2004). After definitive radiation therapy in HNC, the accuracy of combined FDG PET CT to detect residual or recurrent disease seems higher than of contrast enhanced CT. some studies show that specificity of FDG PET CT is higher than contrast enhanced CT (Higgins et al., 2012).

Present series investigated the role of PET CT with regard to response evaluation in 46 patients treated with definitive radiotherapy alone or combination with chemotherapy in whom pre and post treatment PET CT was obtained. FDG PET CT was intended to be done at least three months after completion of radiation therapy as late evaluation was more effective when compared to early evaluation. Present series yielded 91.7% sensitivity and 81.3% specificity after median 20 months of follow up, positive and negative predictive values were 64.7% and 96.3% respectively. Sensitivity and specificity of FDG PET CT is reported to be between 50-88% and 69-93% in different studies (Andrade et al., 2006; Masahiro et al., 2012; Paola et al., 2012; Passero et al., 2010; Prestwich et al., 2012). Of course it is impossible to give exact figures unless all patients undergo surgical resection and thorough pathological examination. Nevertheless median follow up time is reasonable time for occurrence of local or regional relapse for SCCHN therefore prediction of response in present series should not be underestimated.

Overall metabolic complete response as defined by PERCIST criteria was 63% in entire patient population (Masahiro et al., 2012; Passero et al., 2010; Paola et al., 2012). Patients who had residual metabolic activity were closely followed by clinical examination and endoscopic evaluation. In our series two patients had undergone lymph node excision and neck dissection immediately after residual metabolic up take was detected; former was nasopharyngeal cancer and reported to be negative after pathological evaluation and latter was hypopharyngeal cancer and neck dissection revealed residual tumor cells. Although none of the patients with apparent residual up take at primary site on control FDG PET CT was considered to be unsuitable for surgery, 2 patients who had suspicious FDG up take who found to have recurrent disease on their follow up were salvaged with surgery.

In case of metabolic residual disease in the neck, either salvage surgery or histopathological confirmation by means of fine needle aspiration or excisional biopsy is relatively harmless procedures. However in the situation where residual or suspicious metabolic activity is present at primary tumor, it is much difficult to implement organ sacrificing surgery without histological verification. Obtaining histological verification on the other hand is rather difficult especially in laryngeal or hypopharyngeal tumors where residual tumor is usually hidden under normal looking mucosa associated with laryngeal edema. Repeated biopsy attempts in such situation compromise wound healing and may induce radiation necrosis. Therefore we recommend close clinical and radiological follow up rather than taking biopsies in patients with residual metabolic activity (Moeller et al., 2009; Passero et al., 2010; Masahiro et al., 2012; Paola et al., 2012; Prestwich et al., 2012).

Metabolic response rates vary between series this may easily be attributed to tumor site distribution among different studies. High rate of metabolic response occur in patients with nasopharyngeal carcinoma and HPV related oropharyngeal carcinoma. Studies containing high numbers of oropharyngeal carcinoma yield high metabolic response rates (Preswitch et al., 2012). A metabolic complete response rate of 82.8% was observed for patients with nasopharyngeal carcinoma in present series. There were 5 non complete responders in 29 patients with nasopharyngeal carcinoma, of those only one developed local recurrence. However in 17 patients with non-NPC only 5 complete metabolic response (29.4%) was observed 10 of 12 non-complete responders experienced local or regional recurrence. Similarly in a prospective study by Moeller et al patients are divided as high risk (non-HPV, non-oroparyngeal and smoker) and low risk (HPV+, oropharyngeal and non-smoker) response assessment gave significant additional prognostic information for high risk patients. The need of metabolic response assessment is more pronounced in patients with high risk for local failure (Moeller et al., 2009; Esther et al., 2010).

Metabolic complete response is also associated with improved outcome independently from tumor site. Significantly better survival rates were observed in patients with complete metabolic response in present series as well as other studies (Moeller et al., 2009; Passero et al., 2010; Paola et al., 2012; Masahiro et al., 2012) (Figure 1)

Definitely more precise criteria is required for assessment of response, there is no clear cut up take value indicating residual disease, on the other hand repair process of normal tissue may consume glucose which appear as increased up take in control FDG PET CT.

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