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Long Term Negative Predictive Value of Post-Treatment FDG PET/CT Scan in Nasopharyngeal Carcinoma

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Abstract

Objectives: Accurate assessment of response to treatment in Nasopharyngeal Carcinoma (NPC) is important for early administration of salvage therapy and to avoid futile invasive diagnostic investigations. This study assessed the Negative Predictive Value (NPV) of the post-therapy FDG-PET/CT scan throughout a prolonged follow-up period.

Patients and Materials: We reviewed our NPC patients' database from March 2005 to August 2015. A cohort of patients with initial post-treatment negative FDG-PET/CT scan was identified. A scan was considered negative if no non-physiological uptake was seen. Follow-up data was retrospectively analyzed.

Results: Forty-six patients with negative post-treatment PET/CT scans were identified. Median follow-up was 44.1 months. Forty patients were disease-free at last follow-up (e.g., NPV 87%). Mean age at diagnosis of patients who had recurrence was 65.17 years compared to 44.65 years for patients who were disease-free. Based on COX regression analysis, patients who were 65 years old or older had a significant risk for disease recurrence (Hazard Ratio [HR] 10.67, 95% Confidence Interval [CI] 1.95-58.4, p=0.006) compared to younger patients. NPV of patients under 65 was 94% compared to 50% for patients older than 65. Four of six patients who relapsed had T4 disease and the remaining two had T3. There were no recurrences in the group of T1-2 (NPV 100%).

Conclusion: The NPV of PET/CT scans is high and can predict recurrent disease in T1-2 NPC patients and in those younger than 65 years, regardless of T stage. Larger studies are warranted to validate our findings.

Keywords: Nasopharyngeal carcinoma; PET/CT; Follow-up; Recurrence

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Introduction

Nasopharyngeal Carcinoma (NPC) is a distinct form of head and neck cancer with specific geographic distribution, characterized by higher disease incidence in China, Southeast Asia, North Africa and the Middle East. NPC is associated with genetic predisposition, Epstein–Barr Virus (EBV) infection, and environmental factors [1]. Radiotherapy has traditionally been the primary treatment modality for NPC due to its deep location and radiosensitive nature, and adding chemotherapy is indicated for treating advanced disease. Despite excellent Overall Survival (OS) for early stage disease, locally advanced, NPC has a 10% to 15% loco regional relapse rate and a 20% to 30% distant metastasis rate [2,3].

Effective surveillance is key in managing patients with locally advanced NPC after definitive chemoradiotherapy, as early detection of residual, recurrent, and early metastatic disease may improve the likelihood of response and minimize the extent/toxicity of treatment. Both stage at time of diagnosis of recurrence and the interval between initial treatment and recurrence have been shown to have prognostic significance [4]. Options for salvage treatment include re-irradiation, brachytherapy or stereotactic radio surgery, and surgery [5,6].

Radiological anatomical studies, mainly Computed Tomography (CT) and magnetic resonance imaging (MRI), are the mainstay of surveillance imaging. The current guidelines recommend routine annual imaging of the nasopharynx due to its inaccessible location [7]. Positron-emission tomography combined with CT (PET/CT) using the tracer Fluorine -18 Fluorodeoxyglucose (FDG) is increasingly preferred in many institutions for its superior ability to provide information

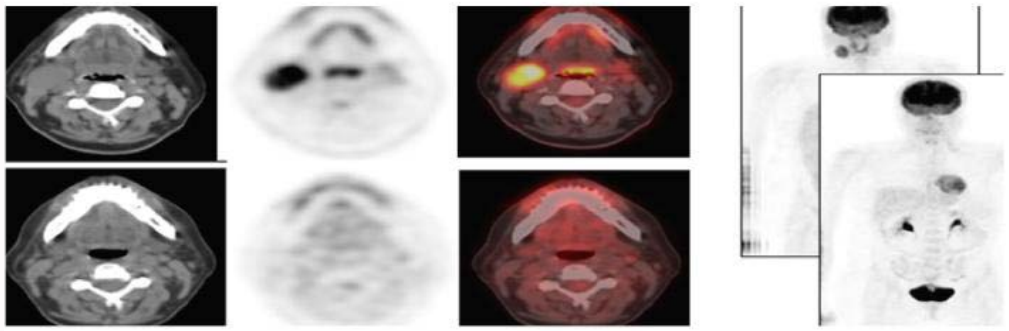

Figure 1: Pre- and post-treatment representative images from PET-CT scan. **a)** Pre-treatment scan showing uptake in the cervical lymph node. **b)** Post-treatment scan without the uptake in the neck. **c)** Pre-treatment scan showing uptake in the nasopharynx. **d)** Post-treatment scan without the uptake in the nasopharynx.

about biologic function. A particular advantage in NPC is realized due to its high accuracy in cervical lymph node detection, as well as the ability to discriminate local post-therapy fibrotic changes from residual or recurrent disease [8]. Meta-analyses of PET/CT studies involving patients with squamous-cell carcinoma of the head and neck after chemoradiotherapy have shown high Negative Predictive Values (NPV) of 94.5% to 96.0% [9,10]. However, in the majority of the studies included in the meta-analyses, median follow-up time was either not reported or was too short to allow for extrapolation of the results.

The aim of this study was to assess the long-term utility of a negative initial post-treatment PET/CT scan in evaluating response to chemoradiotherapy in patients with locoregionally advanced NPC, namely to identify patients with metabolic complete response who are unlikely to recur *vs.* those whose risk of recurrence is higher.

Patients and Materials

Study population

In this retrospective study, we reviewed the medical records of patients with locoregional NPC who were treated at our institution between March 2005 and August 2015. Before treatment, a medical history was taken and patients underwent physical examination, complete blood count, blood biochemistry, and fiber optic nasopharyngoscopy. Imaging modalities used for disease staging included PET/CT and MRI scans.

This study was approved by the Institutional Review Board (IRB) and was granted a waiver for obtaining patient consent due to its retrospective design.

PET/CT scans

Patients were instructed to undergo a surveillance PET/CT scan after 12 weeks from their last treatment session in order to minimize false positive rates. The median time of obtaining a scan in our study population was 11 weeks. A negative PET/CT scan was defined as a scan with no area of focal ^{18}F-FDG activity of intensity higher than that of the surrounding tissues and unrelated to normal physiologic or benign ^{18}F-FDG uptake (Figure 1).

All patients in this study underwent a surveillance PET/CT scan at the end of their treatments. Patients were instructed to fast for at least four hours prior to injection (with the exception of non-sweetened fluids). Blood glucose levels ≥ 200 mg/dL were required. Patients were injected with 14 millicurie ^{18}F-FDG, and PET/CT scans were performed 90 min after injection with immobilization of the head and neck region. An integrated system was used for scanning

Table 1: Demographics and Clinical Characteristics of the Entire Cohort.

%	No. of patients		Variable
100	46	47.3 (13-82)	Median age (range), y
72	33	Male	Gender
28	13	Female	
72	33		Pre-treatment PET-CT scan
45.2	9	T1	T stage
33.3	15	T2	(n=45)
26.6	12	T3	
20	9	T4	
17.3	8	N0	N stage
30.4	14	N1	(n=46)
47.8	22	N2	
4.3	2	N3	
16.2	7	II	Stage
58.1	25	III	(n=43)
20.9	9	IV a	
4.6	2	IV b	
100	455	44.1 (5-111)	Median follow-up (range), month

(GE Discovery LS, GE, and Milwaukee WI, USA) with non-contrast enhanced CT imaging. The PET/CT scan specifications were: imaged Field of View (FOV), 14.5 cm; time/FOV, 4 min; slice thickness, 4.25 mm; X-ray tube voltage, 140 kV; tube current–time product, 90 mA; pitch, 0.75:1; rotation speed, 0.8 sec/rotation. PET/CT reconstruction was performed using the OSEM algorithm [11]. PET/CT scans were interpreted locally by PET/CT specialty radiologists and nuclear medicine physicians. Scans before and after chemoradiotherapy were compared with respect to primary tumor region, cervical lymph nodes, and distant metastatic sites.

Follow-up

The follow-up period was defined as the time interval between the first PET/CT scan after treatment and the earlier of last visit or recurrence. Date of last follow-up was August 2016. Patients were followed and monitored both by a head and neck oncologist and an otolaryngologist. Patients were seen by the two physicians every three months in the first year and every four months thereafter. Complete physical examination and a fiber optic nasopharyngoscopy were performed at each visit.

After the first PET/CT scan post-treatment, patients underwent

annual surveillance PET/CT scans. If three consecutive scans were normal, patients were monitored subsequently by clinical inspection and fiber optic endoscopy without further imaging studies, unless there were clinical indications of recurrence.

Outcomes

Our primary outcome was NPV of the first PET/CT after treatment. We defined NPV as the ratio between the number of patients whose first PET/CT scan after treatment was negative and who remained disease free until last follow-up and the overall number of patients whose first PET/CT scan after treatment was negative. We used this definition, hypothesizing that negative scans may indicate a complete metabolic shut-down of the disease in NPC patients and, thus, a cure/long-term remission, unlike other diseases (e.g., breast cancer, small-cell lung cancer) where negative PET/CT scans frequently indicate short-term remission.

Statistical analysis

Descriptive statistics were used to summarize patient and tumor characteristics. Cox regression univariate model was performed. Kaplan-Meier analysis was used to estimate 3 year Disease Free Survival (DFS).

Results

Study population and treatments received

Overall, the medical records of 72 patients were reviewed, 46 of whom had a negative post-treatment PET/CT scan and were included in the current analysis. Table 1 presents the baseline characteristics of our cohort. Median (range) age of patients at diagnosis was 47.3 (13-82) years. Thirty-three patients in the cohort also had a PET/CT scan for staging.

Induction chemotherapy was administered to 41 (90%) patients. Thirty-seven patients received neoadjuvant chemotherapy with intravenous cisplatin (100 mg/m^2, day 1) and a continuous infusion of fluorouracil (1000 mg/m^2 per day, day 1 to day 5) every three weeks, for three cycles. Three patients received carboplatin (6 AUC mg/mL/min) and a continuous infusion of fluorouracil (100 mg/m^2, days 1-5) every three weeks, for three cycles. One patient received intravenous docetaxel (75 mg/m^2, day 1), cisplatin (75 mg/m^2, day 1) and continuous fluorouracil (750 mg/m^2 per day, day 1 to day 5) every three weeks, for three cycles.

External beam radiotherapy to the primary tumor and bilateral cervical lymph nodes combined with platinum-based chemotherapy was initiated 3 weeks to 4 weeks after completion of induction chemotherapy. Five patients were treated with upfront concurrent chemoradiotherapy. Twenty-eight patients received radiation therapy using Intensity-Modulated Radiation Therapy (IMRT) technique, 13 patients by 3-D, and the remaining five by 2-D technique. Radiotherapy was administered as 2.0 Gy daily fractions using 6 MV photon beams (Elekta) five days per week, for a total dose of 70 Gy for Gross Target Volume (GTV), 60 Gy to 66 Gy for Clinical Target Volume (CTV) of high risk, and elective nodal irradiation involved radiation doses of 50 Gy. Overall, 44 (96%) patients underwent concomitant chemoradiotherapy: 41 patients received cisplatin (40 mg/m^2 every week) and three received weekly carboplatin (2 AUC mg/mL × min).

Clinical outcomes

Data were available for all patients in the cohort. Date of last follow-up was August 2016. During a median (range) follow-up period of 44.1 (5-111) months, 40 patients remained disease-free. The calculated NPV for our whole study population was 87%. Six (13%) patients experienced disease recurrence; median (range) time from the first PET/CT after treatment to recurrence was 24.5 (7-33) months. Three patients had local recurrence, one had locoregional recurrence and two had recurrent metastatic disease. Five of the six patients experienced recurrence after 12 months from the first PET/CT scan post-treatment. All these six patients received induction chemotherapy followed by chemoradiotherapy. The mean age of patients who remained disease-free was 44.7 (SD 16.6) years' *vs.* 65.2 years (SD 16.2) for the patients who relapsed. We further divided our patients into two subgroups based on age at diagnosis; the NPV of the PET-CT scans for patients who were <65 years at diagnosis was 94% *vs.* 50% for those who were 65 and older at diagnosis.

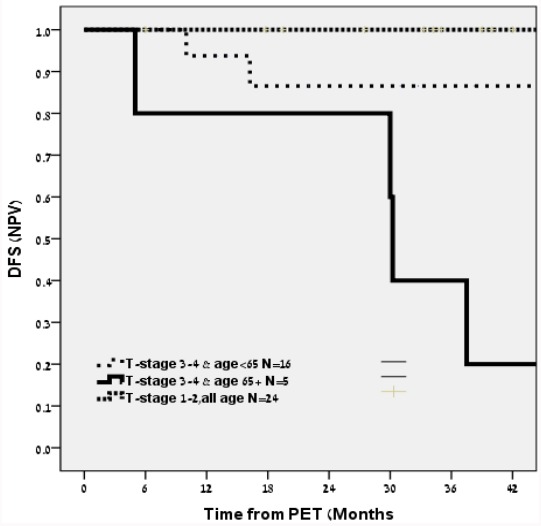

Figure 2: Kaplan-Meier survival analysis according to age and stage at diagnosis.
Disease free survival comparison between stage T1-2, all ages (dark dashes), T3-4, age <65 years (light dashes), and T3-4, age >65 years (solid line).

Table 2: Patients with Recurrent Nasopharyngeal Carcinoma.

TTR (months)	N stage	T stage	Age (y)	Patient
32	N1	T4	83	P1
7	N0	T4	77	P2
33	N2	T4	70	P3
19	N0	T4	37	P4
30	N2	T3	65	P5
10	N1	T3	59	P6

TTR: Time to Recurrence from last treatment

COX regression analysis demonstrated that age at diagnosis was an independent risk factor for disease recurrence. Patients <65 years at diagnosis had a significant risk for disease recurrence (Hazard Ratio [HR] 10.67, 95% Confidence Interval [CI] 1.95-58.4, p=0.006). All six patients who experienced recurrence had T3 (two patients) or T4 (four patients) primary tumors. The nodal status of these six patients was homogeneously distributed between N0 and N2 (Table 2). No recurrences were reported in T1-2 patients. Additional univariate analyses based on N-stage, mode of radiotherapy, and induction chemotherapy were not statistically significant for disease recurrence.

Based on these results, patients were categorized into further

subgroups based on age at diagnosis and T stage. The Three-year DFS was 86.5% for patients <65 years at diagnosis with T3-4 disease compared with a 3-year DFS of 40% for patients >65 years at diagnosis with the same T category (HR 7.06, 95% CI 1.29-38.74, p=0.024) (Figure 2).

Discussion

Response to radiotherapy is assessed by clinical/imaging evaluation, including physical examination, fiber optic nasopharyngoscopy, and imaging studies (CT, MRI), which determine differences in tumor sizes. However, determining response based solely on imaging studies may not suffice as the decrease in tumor volume may be delayed (despite a response), and because CTs/MRIs are limited in their ability to differentiate between a response and radiotherapy-induced fibrosis or necrosis, as well as by their ability to detect metastases in lymph nodes that are not enlarged [12,13].

The value of PET/CT *vs* regular CT/MRI has been previously examined. One study demonstrated that PET/CT has high NPV (99%) and a significant prognostic value, and another study showed sensitivity, specificity, and accuracy of 100%, 93% to 98%, and 94% to 98%, respectively [13,14]. In contrast, the value of PET/CT over other imaging approaches was found only for a subset of high-risk patients in another study [15]. Notably, in most of these studies, sample size was small and the cohort was diverse with respect to head and neck tumor types, and the timing of the CT/MRI performed. The potential role of imaging studies and the most appropriate timing for them is yet to be determined (per tumor type).

Assessing response to radiotherapy is a key element in NPC patients, as it allows treating non-responders with life-saving therapies while avoiding unnecessary invasive procedures in the responders. Although NPV was quite high in our study (87%), it is lower than that suggested in the available literature. For example, Yen and colleagues evaluated 39 patients with stage 4 NPC who underwent PET/CT before as well as three months after completing chemoradiotherapy and found NPV of 100% for local residual/recurrent disease after a follow-up period of 24.2 ± 9.5 months (PET/CT was defined as positive for standardized uptake values [SUVs] >4) [16]. We assessed the PET/CT results visually (e.g., not by SUV), defining every local/regional uptake above background as residual/recurrent disease, and found NPV of 87% after a median follow-up of 44 months. The lower NPV observed in our study probably stems from the longer follow-up. Other studies that assessed results beyond completing chemotherapy had shorter median follow-up times of 16 and 24 months [16,17].

Notably, similar to our approach, other studies also used visual assessment of PET/CT. For example, in a study by Law et al., [18] examining 21 NPC patients who underwent PET/CT before and 3 months to 5 months after treatment, response by PET/CT was determined visually and was defined as absence of pathological uptake that was observed at diagnosis (follow-up to determined false positivity was three months, false negativity was 12 months).

High NPV of PET/CT for confirming response in the primary tumor is particularly important in NPC, as identifying residual/recurrent local disease by CT may be difficult due to local post-treatment changes and the risks involved in performing another biopsy. The longer follow-up in our study which, as expected, led to lower NPV, constitutes strength, as it demonstrates the long-term prognostic value of a negative PET/CT scan. High NPV of PET/CT for NPC would facilitate identifying low-risk patients whom may not require any further investigations and high-risk patients for whom more aggressive management or early salvage treatment may be warranted. In our cohort, the PET/CT scan had a high NPV in patients with primary T1-2 disease, regardless of nodal states. In fact, none of the patients (n=24) with T1-2 and a negative post-treatment PET/CT scan recurred during the follow-up period. Thus, these data suggest that less intense follow-up for this group of low-risk patients may suffice and that these patients may be spared unnecessary PET/CT scans and their associated cost and inconvenience to the patients. On the other hand, the NPV of PET/CT scans for patients with locally advanced disease (T3-4), especially those >65 years old, were low. This subgroup of patients had worse prognosis (with respect to PFS and OS). Thus, we might consider close follow-up for this subgroup in order to diagnose recurrence even in subclinical stages. Early detection of recurrence allows for localized treatment, such as stereotactic radiotherapy or surgery with achieving negative margins.

Our study is limited by its retrospective nature, relatively small sample size, and a qualitative rather than a quantitative interpretation of the PET/CT scans. Notably, performing such a study with a larger sample size is challenging, as this malignancy is relatively uncommon and its cure rate is high (i.e., small number of events is expected).

Conclusion

The NPV of the initial post-treatment PET/CT scan proved to be highly valuable, especially for young patients with T1-2 disease, and could be added to the prognostic parameters in NPC patients.

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