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Review

Use of ^{18}F-FDG PET/CT in the Diagnosis, Staging, Response Assessment and Prognosis of Nasopharyngeal Carcinoma: an Updated Review

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Abstract: Nasopharyngeal carcinoma (NPC) is endemic in southern China and part of Southeast Asia. The main treatment for nasopharyngeal carcinoma is radiotherapy. The accurate diagnosis of the tumor extension and the delineation of target volume mostly depend on imaging. The imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT), which provides both anatomic and biological information of tumor, plays an important role in the management of NPC. With the help of ^{18}F-FDG PET/CT, a better diagnosis of cervical nodal involvement and distant metastasis has a great impact on radiotherapy planning and treatment strategy. ^{18}F-FDG PET/CT image provides additional biological information, to help in differentiating the post-radiation inflammation and local residual/recurrent disease. For locally advanced disease, ^{18}F-FDG PET/CT is a better and more sensitive approach for the assessment and surveillance of therapeutic response of NPC , as well as detecting of early relapses and metastasis, , compared with conventional workup. Various PET/CT parameters have been correlated with response and survival. Higher ^{18}F-FDG uptake has been proven to predict poorer response and worse outcome. The combination of EBV DNA copies and PET/CT scan seems to be a useful and effective strategy in the follow-up of NPC.

Keywords: Nasopharyngeal Carcinoma; ^{18}F-FDG; PET/CT; Diagnosis; Staging; Response Assessment; Prognosis

JNPC Journal of Nasopharyngeal Carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) is endemic in southern China and part of Southeast Asia [1]. In southern China, the prevalence is > 20/100,000 person-years [2]. Owing to the specific anatomic location and highly responsive to radiation, the main treatment for NPC is radiotherapy. It is difficult to obtain the information of tumor extension by pathology. The accurate diagnosis of the tumor extension and the delineation of target volume mostly depend on imaging. Magnetic resonance imaging (MRI) has a good capacity to depict the detailed anatomic information and has been widely used in the management of NPC. However, MRI only provides anatomic and volumetric information, and does not reveal the biological status of tumor cells. The advent of positron emission tomography (PET/CT), especially ^{18}F-fluorodeoxyglucose PET/CT has facilitated the anatomic and biological assessment of the tumors. Various studies demostrated that ^{18}F-FDG PET/CT imaging had been actively integrated with the management of NPC. The purpose of this article is to review the role of ^{18}F-FDG PET/CT in staging, response assessment, diagnosis of residual diseases, predicting outcome and post-treatment surveillance of NPC.

Initial Staging

The staging of NPC has a major influence on treatment strategy. In early cases, radiotherapy is enough to control the disease. In locally advanced disease (III-IVb), concurrent chemoradiotherapy is the main treatment modality, whereas the value of neoadjuvant chemotherapy and adjuvant chemotherapy is still in debate. In cases with distant metastasis, chemotherapy is the main treatment and radiotherapy will give according the response to chemotherapy. Accurate staging and diagnosis of tumor extension is very important for treatment strategy and target volume delineation.

Local invasion

MRI is commonly used in assessment of local involvement of NPC, which can clearly show the involvement of soft tissue, bone as well as the intracranial lesion [3, 4]. On the contrary, ^{18}F-FDG PET/CT appears to be inferior to MRI for assessment of local invasion, such as the involvement of parapharyngeal space, skull base, and intracranial lesions [5, 6]. Owing to the high glucose metabolism of brain tissue, it is hard for ^{18}F-FDG PET/CT to clearly distinguish the intracranial extension. Using the MRI as a reference, Lim [7] et al reported that ^{18}F-FDG PET/CT could only detect 42.7% of intracranial invasion. King reported [5] that ^{18}F-FDG PET/CT undermapped the extent of local invasion in approximately half of patients. Ng [6] demonstrated that ^{18}F-FDG PET/CT downstages 22.5% of patients with regards to T staging. On the other hand, ^{18}F-FDG PET/CT could not identify some early tumor involvement of nasopharyngeal mucosa, due to a low tumor burden.

Retropharyngeal lymph node metastasis

The involvement of retropharyngeal lymph nodes are frequently seen in NPC, presented in 72% of patients with NPC and 94% of all patients with nodal disease [7]. The diagnosis of involvement of retropharyngeal nodes on imaging has been based on the axial diameter of nodes, the presence of necrosis and enhancement. Mancuso et al. [8] found that the maximum diameter of retropharyngeal nodes in normal people identified by CT was 5 to 8 mm in young adults and 3 to 5 mm in adults. A recent MRI study by Lam et al. [9] in Chinese population found that normal retropharyngeal nodes were smaller than 4 mm in the maximum diameter of the shortest axis. Based on these studies, Lam and King et al [8, 10] suggested that over 4-5mm size in the shortest axis of nodes was used as the diagnostic criteria for an abnormal retropharyngeal node. A study by Tang et al. [10] has compared the diagnostic value of PET/CT and MRI in retropharyngeal nodes in NPC. The detection rates of retropharyngeal lymph node

JNPC Journal of Nasopharyngeal Carcinoma

metastasis by MRI was significantly higher than that by PET/CT (44.8% vs. 24.1%, p<0.001). The maximum standard uptake value (SUV_{max}) of PET/CT was positively correlated with the minimal axial diameter of retropharyngeal lymph node. There were only 5.8% of nodes with a SUV_{max} greater than 2.5 for retropharyngeal lymph nodes with axial diameter < 10mm. In retropharyngeal nodes ≥10 mm in diameter, the percentage rose to 88.2% [11] [please offer references here]. Therefore, PET/CT is inferior to MRI in demonstrating tumor involvement in retropharyngeal nodes, especially in nodes with shortest diameter smaller than 10 mm. Moreover, PET/CT failed to identify retropharyngeal nodes when they were close to or merged with primary tumors [5, 6]. It yielded false-positive results in cases of direct bulky parapharyngeal invasion as well [6].

Cervical lymph node metastasis

The metastasis of cervical lymph nodes is frequent in NPC. It has been reported that 60%-88.1% of patients have regional nodal involvement at presentation [11-14]. The diagnosis of cervical nodal metastasis has an influence on the planning of radiotherapy as well as the modification of treatment strategy. The diagnosis of cervical nodal involvement by MRI is often based on nodal size, the presence of necrosis and enhancement. Several studies have compared the accuracy of PET/CT and MRI to diagnose cervical nodal metastasis in head and neck cancers [15-19]. PET/CT is generally more sensitive than MRI to detect nodal metastasis, with a sensitivity of 74.7%-96.5%, whereas the sensitivity of MRI is 52.6%-93%.However, there is no significant advantage of PET/CT in specificity, with a specificity of 87%-98% (the specificity of MRI 79%-95%). To our best knowledge, there are four studies comparing the diagnostic efficacy of PET/CT and MRI in NPC [5, 6, 20, 21]. In three out of four studies [6, 21, 22], PET/CT yielded a higher accuracy in diagnosing cervical nodal involvement. With PET/CT images, metastasis in morphologically benign lymph nodes may be correctly identified and the false metastatic lesions in enlarged lymph nodes may be excluded. In general, ^{18}F-FDG PET/CT is a highly sensitive and accurate tool to detect cervical nodal metastasis, which influences the N stage and the planning of radiotherapy. However, ^{18}F-FDG PET/CT still yields a low percentage of false-positive and false-negative. Most of the false-positive cases were proved to be inflammatory hyperplasia [6] and most of false negative cases were micro-metastases in cervical nodes less than 1 cm in diameter [23, 24].

Distant metastasis

In regards to diagnosis of distant metastasis, several studies have concordantly shown that PET/CT is more accurate than conventional workup such as chest radiography, chest CT, abdominal ultrasound and bone scan [25-27]. Yen reported [28] that PET/CT could detect additionally 12.9% of distant metastasis, among patients diagnosed as M0 by conventional workup. The patient-based sensitivity and specificity of ^{18}F-FDG PET for distant metastases were 100% and 86.9%, respectively. Chang et al. [29] demonstrated that the sensitivity and specificity of ^{18}F-FDG PET for distant metastases were 100% and 90.1%. In another study by Liu [30] et al., ^{18}F-FDG PET was found to be more effective than conventional workup. On region-based analyses, ^{18}F-FDG PET was more sensitive than skeletal scintigraphy [27, 31] and chest radiography [27] for detecting bone metastases and pulmonary metastases, respectively. In addition, ^{18}F-FDG PET/CT was more sensitive to detect distant nodal metastasis [15]. The frequencies of mediastinal and abdominal nodal metastasis were 4.5% and 3.4%, identified by ^{18}F-FDG PET/CT [15. All these cases were associated with supraclavicular fossa node involvement, and might represent the further caudal lymphatic spread of NPC beyond the supraclavicular nodes. These metastases were often missed by conventional workup, thus PET/CT has completely changed the treatment strategy from radiotherapy to chemotherapy.

In a word, ^{18}F-FDG PET/CT played a significant role in determining cervical nodal metastasis and distant metastasis. Considering patients with a N3 disease have a significantly greater risk of distant metastasis [4], we recommend ^{18}F-FDG PET/CT for staging, especially in N3 stage for NPC patients.

Diagnosis of local recurrence and residual lesions

Persistent or recurrent disease at primary site

Radiation, after radiotherapy of NPC, causes inflammatory reaction, distorting of the anatomic structures and the growth of scar tissue [32] [please offer references here]. These changes make the diagnosis of persistent or recurrent disease more difficult. MRI was commonly used in determining local recurrence and persistent lesions. However, false positive were noted due to the inflammatory reaction and anatomic distortion. Thus, scholars tried to integrate ^{18}F-FDG PET/CT with the diagnosis of recurrence and residual disease. To our best knowledge, four studies [29-32] used both ^{18}F-FDG PET and MRI in determining recurrence of NPC. Two studies [33, 34] showed no false negative and few false positive, resulting in a sensitivity of 100% and specificity of 92.9%- 93.4% of PET/CT. However, in another study [35], the sensitivity and specificity of ^{18}F-FDG PET for the detection of recurrent NPC at the primary site were 91.6% and 76.0%, respectively, with 1 false negative and 6 false positive. In the report of Comoretto [36], there was a trend toward greater accuracy of MRI over PET/CT in detecting residual and/or recurrent NPC at the primary site (92.1% for MRI vs. 85.7% for PET/CT, p=0.16). In these studies [31, 32], the false positive cases of PET/CT were attributed to subacute/ chronic inflammation, while false negative cases of PET/CT were due to superficial involvement of mucosa or intracranial invasion. Comoretto suggested that the advantage of MRI over PET/CT was probably attributed to the following reasons: MRI provided additional information in assessing skull base involvement and intracranial invasion while FDG PET/CT was not considered a trustworthy method for the study of the intracranial disease due to the physiologically high FDG uptake by brain; MR imaging examination was subjected to a dynamic contrast-enhanced study that could facilitate differentiation between fibrosis and residual disease [37]. Moreover, it is worthwhile to note that radiation induced necrosis could be present with significant uptake of FDG [35, 38], which could be misdiagnosed by both MRI and PET/CT [39]. In consideration of advantages and pitfalls of both techniques, we recommend using both MRI and ^{18}F-FDG PET/CT in determining local recurrence and residual disease. Close clinical follow-up and biopsy are warranted to confirm the diagnosis.

Persistent or recurrent disease at cervical lymph nodes

In terms of the diagnosis of recurrent or persistent cervical nodes, ^{18}F-FDG PET/CT appears to add significant information to MRI findings. Ng [31] reported the sensitivity and specificity for detecting recurrent and residual nodal diseases by PET/CT was 90.0% and 88.9%. Comoretto [32] reported that the sensitivity and specificity for PET/CT in depicting residual and recurrent nodal diseases were 95.2% and 97.6%, while the sensitivity and specificity for MRI were 90.5% and 90.5%. No significant difference was observed between MRI and PET/CT (p=0.08). Both the studies demonstrated that ^{18}F-FDG PET/CT were a highly sensitive and accurate tool to detect nodal diseases. However, some problems should be taken into consideration. ^{18}F-FDG PET may not be sensitive enough to detect micro-metastases in nodes [23, 24]. At this time, neither anatomic nor metabolic imaging provides sufficient resolution power for the detection of microscopic lesion [40]. On the other hand, the false positive cases of ^{18}F-FDG PET/CT were mostly due to inflammatory hyperplasia of lymph nodes [32].

Therapeutic response assessment

Although intensity modulated radiation therapy (IMRT) has brought significant improvement in overall survival of NPC, a certain part of patients develop local recurrence. Once recurrence, the outcomes is poor and the quality of life is bad. Therefore, it is urgent to develop a way to predict treatment response before its onset, to allow a more aggressive treatment strategy.

Conventional imaging such as CT and MRI are used in current clinical practice for response assessment. However, there are some pitfalls of these techniques. CT and MRI are used to measure the anatomic volume changes of the tumor, which would delay after chemotherapy and radiotherapy. In addition, they cannot differentiate residual tumor from inflammation and fibrosis from surround normal tissue [41-43]. Functional imaging such as ^{18}F-FDG PET/CT has been introduced in treatment response assessment since it could provide additional biologic information. ^{18}F-FDG PET/CT has been used to evaluate treatment response in various malignancies, including esophageal cancer, lung cancer, colorectal cancer, et al [44-47]. To our knowledge, there are very few studies focusing on treatment response assessment of NPC. In a study of T4 NPC reported by Yen et al [48], the baseline and post-treatment (3 months post-chemoradiation) SUV_{max} correlated with local response. There is a trend of difference of baseline SUV_{max} between responders (patients with local residual disease) and non-responders (patients without local residual disease). The decrease in SUV_{max} between baseline and 3 months post-chemoradiation were 62.9% for non-responders and 76.1% for responders. Non-responders had a significantly higher post-treatment SUV_{max} than the responders, with a cutoff value of SUV_{max} less than 4. Xie et al [49] demonstrated that patients who had a complete metabolic response (CMR) measured by FDG uptake at 1–5 months after radiotherapy had a higher overall survival (OS) than those who exhibited a partial metabolic response (PMR). Chan et al [50] performed a study to investigate the prognostic implication of post-chemoradiation PET/CT in locally advanced NPC patients. The results showed that PET finding of 3 months post-chemoradiation and total lesion glycolysis were independent prognostic factors of OS and disease-free survival (DFS). Post-therapy PET imaging at 3 months was more predictive of DFS than conventional workup and TNM stage. It is worthwhile to note that the difference between DFS of complete responders and non-complete responders evaluated by conventional workup did not reach a statistical significance in IVa-IVb NPC patients. Detailed analysis showed that conventional workup failed to detect 43% of therapeutic failures, including locoregional failure and distant metastasis of solitary organ sites. The follow-up of PET/CT in locally advanced NPC was more sensitive to detect early failure and hence changed the treatment strategy for them. Taken together, PET/CT appeared to be a more sensitive approach for surveillance of post-treatment NPC, especially for IVa-IVb patients.

Prognosis

Despite the application of IMRT and chemotherapy, there are occasions of local failure and distant metastasis. The identification of prognostic factors would be helpful in risk stratification and tailoring the treatment strategy for the high-risk patients, such as higher radiation dose or more aggressive chemotherapy. ^{18}F-FDG PET/CT has been investigated in prognosis of various malignancies, and the uptake of ^{18}F-FDG has been correlated with aggressive behavior and poor prognosis [51-54].

Recently, several studies have reported the prognostic value of ^{18}F-FDG PET/CT of OS and DFS in NPC. In a study by Lee et al [55], ^{18}F-FDG-PET uptake, as determined by calculating SUV_{max}, is a valuable tool to evaluate prognosis in NPC patients receiving concurrent chemoradiotherapy. The study also suggested that

JNPC Journal of Nasopharyngeal Carcinoma

SUV_{max} of the node higher than that of the primary site and SUV_{max} of 8 or higher were associated with poorer prognosis. Xie et al [56] demonstrated that locally advanced NPC patients with an pretreatment SUV_{max} below 8.0 had a significantly better OS and DFS than patients with an SUV_{max} above 8.0. The patients who showed with PMR had a significantly lower 5-year OS and DFS than patients with CMR at 1-5 months after radiation. Similarly, Chan et al [57] reported that both SUV_{max} of primary tumor and metastatic nodes were independent predictors of DFS of NPC patients as well. Significantly better DFS was found in patients with primary tumor SUV_{max}<7.5 and nodal SUV_{max} <6.5, respectively.

Interestingly, other studies suggested that pretreatment SUV_{max} are more related to distant metastasis. As Chan reported [58], SUV_{max} on ^{18}F-FDG represented an important independent prognostic factor for distant recurrence, more predictive than traditional TNM stage. A SUV_{max} > 12.0 indicated significantly poorer distant control. Then a further investigation [59] with a larger sample size (196 NPC patients with III-IV disease) demonstrated that a high SUV_{max} of neck lymph nodes independently predicted distant failure-free survival (DMFS) and a higher total lesion glycolysis independently predicted OS and DFS. In a study enrolling 371 NPC patients treated with IMRT [60], patients with a lower SUV_{max} of primary tumor and metastatic lymph nodes had a significantly better 5-year DMFS but show no significance in local or regional control. The SUV_{max} of the primary tumor and neck lymph nodes were independent prognostic factor of DMFS in NPC patients treated with IMRT.

Such discrepancies can be related to different inclusion criteria, to different number of patients recruited and to the change of failure patterns due to IMRT. With the advent of IMRT and the application of chemotherapy, the locoregional control of NPC has been greatly improved. The main failure pattern is distant metastasis. Detailed studies of TNM stages have shown that T stage failed to predict local recurrence rate when IMRT was delivered [61, 62], whereas notable differences were observed among the distant metastasis rate of N0-N3 disease [63]. According to the report by Sun [59] et al, the DMFS of N0, N1, N2 and N3 were 96.8% 85%, 73.5% and 62.1% ($p<0.001$), respectively. Thus, the higher metabolic activity of tumor, especially the higher SUV_{max} of the metastatic lymph nodes might reflect a more aggressive metastatic potential, which correlated with distant metastasis.

In addition, PET/CT parameters other than SUV_{max} have been received more and more attentions in the prognosis of solid cancers [64-69]. SUV_{max} is a semiquantitative index and can be influenced by the volume of interest which is visually delineated on side-by-side analysis with CT or MRI under most circumstances. Metabolic tumor volume (MTV), defined as the volume of tumor tissues with increased FDG uptake, usually measured from PET/CT images by automatic contouring methods, is theoretically a better predictor of outcome than SUV_{max} [65]. Total lesion glycolysis represents metabolic activity throughout the entire tumor above a minimum threshold [69], might reflect the metabolic burden better than SUV_{max}. In a study [60] to evaluate the predictive value of MTV of pharyngeal carcinomas, most of the cases (76.8%) were nasopharyngeal carcinoma. MTV was shown to be the only significant predictor of short-term response and DFS, with a cutoff value of MTV≤ 40ml by multivariate analysis. SUV_{max} failed to reach a statistical significance to predict response and DFS. In the study by Chan [55], a high SUV_{max} of neck lymph nodes independently predicted DMFS and a higher total lesion glycolysis independently predicted OS and DFS. A better predictive value of MTV and total lesion glycolysis of OS and DFS has been proved in other head and neck cancers [60-62], lung cancer [63], breast cancer [64], et al.

Location of NPC relapse

Numerous studies have shown the circulating EBV DNA levels correlated with treatment outcome. Pretreatment EBV DNA copies are a good prognostic factor for NPC. In most patients, the EBV DNA copies drops to baseline after radiotherapy. The rise of EBV DNA copies during follow-up usually precedes the relapse of disease. Since both EBV DNA copies and ^{18}F-FDG PET/CT have the predictive potential, there have been some efforts in combing these two parameters.

Mäkitie et al [68] performed the first study combing EBV DNA copies and ^{18}F-FDG PET/CT in response evaluation and prognosis prediction. The results showed that reduction in EBV DNA copies and normal PET scans after treatment were consistent among patients who had residual abnormality on MRI. Persistent elevated EBV DNA copies and abnormal PET scans after treatment suggest residual disease. Ma et al [69] tried to explore the relationship between EBV DNA copies and metabolic activity in NPC. The study revealed significant correlation between pretreatment SUV_{max} of primary tumor and pretreatment EBV DNA copies, but further regression analysis did not confirm a significant association between them. Wang et al [57] investigated the combination of plasma EBV DNA copies and ^{18}F-FDG PET scan in the detection of recurrent nasopharyngeal carcinoma. In this study, all the patients were monitored by an EBV DNA assay every 3-6 months. ^{18}F-FDG PET scan was performed once the abnormal EBV DNA copies or clinically suggestive signs of recurrence were noted. The plasma EBV DNA assay correctly predicted all NPC recurrences, and PET had high capacity to localize potential lesion sites. The sensitivity and specificity of PET/CT to detect relapse lesion were 81.8% and 77.1%, respectively. The screening of EBV DNA and location of recurrence by PET/CT appeared to be a useful and effective way of follow-up in NPC patients.

Conclusion

Taken together, ^{18}F-FDG PET/CT has played an instrumental role in the management of NPC. ^{18}F-FDG PET/CT may sensitively determine cervical nodal metastasis and distant metastasis. With the help of ^{18}F-FDG PET/CT, a better diagnosis of cervical nodal involvement and distant metastasis has a great impact on treatment strategy and radiotherapy planning. ^{18}F-FDG PET/CT provides additional biological information, which helps to differentiate the post-radiation inflammation and local residual/recurrent disease. For locally advanced disease, ^{18}F-FDG PET/CT appears to be a better and more sensitive approach for therapeutic response assessment and surveillance, and detecting of early relapses and metastasis of NPC, compared with conventional workup. However, ^{18}F-FDG PET/CT is inferior to the MRI in the T staging and identifying the metastasis of retropharyngeal nodes, ^{18}F-FDG PET/CT still yields a low percentage of false-positive and false-negative due to be inflammatory hyperplasia and micro-metastases in cervical nodes.

Various PET/CT parameters, including SUV_{max}, MTV and total lesion glycolysis have been correlated with response and survival. There is some evidence suggesting MTV and total lesion glycolysis are better indexes to reflect tumor burden and predict OS and DFS. The combination of EBV DNA copies and PET/CT scan seems to be a useful and effective strategy in the follow-up of NPC.

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