MINIREVIEWS

Positron-emission tomography/computed tomography imaging in head and neck oncology: An update

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Abstract

Cancers of the head and neck account for more than half a million cases worldwide annually, with a significant majority diagnosed as squamous cell carcinoma (HNSCC). Imaging studies such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}F-2-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) are widely used to determine the presence and extent of tumors and metastatic disease, both before and after treatment. Advances in PET/CT imaging have allowed it to emerge as a superior imaging modality compared to both CT and MRI, especially in detection of carcinoma of unknown primary, cervical lymph node metastasis, distant metastasis, residual/recurrent cancer and second primary tumors, often leading to alteration in management. PET/CT biomarker may further provide an overall assessment of tumor aggressiveness with prognostic implications. As new developments emerged leading to better understanding and use of PET/CT in head and neck oncology, the aim of this article is to review the roles of PET/CT in both pre- and post-treatment management of HNSCC and PET-derived parameters as prognostic indicators.

Key words: Positron emission tomography; Staging; Diagnosis; Computed tomography; Head and neck cancer; Management of squamous cell carcinoma; Carcinoma of unknown primary; Second primary malignancy; Surveillance; Recurrence; Prognosis

Core tip: In the pre-treatment phase, positron-emission tomography/computed tomography (PET/CT) is valuable in the evaluation of patients with carcinoma of unknown primary origin, detection of synchronous second primary tumor, staging of cervical lymph node metastasis and assessment for distant metastases. In the post-treatment

phase, PET/CT is helpful in evaluating treatment response, detecting residual or recurrent tumor and excluding distant metastases. Prognostic factors derived from PET/CT metabolic and functional data are useful in predicting tumor aggressiveness with implication on patient's survivability, and facilitate selection of treatment modality and personalized treatment options.

INTRODUCTION

Cancers of the head and neck account for more than half a million cases worldwide annually, with a significant majority diagnosed as squamous cell carcinoma (HNSCC). The incidence of head and neck cancer in the United States is approximately 3% of all new cancer cases, accounting for almost 60000 cases each year and 12000 deaths from the disease[1]. Tobacco and alcohol abuse, human papillomavirus (for oropharyngeal cancers), and Esptein-Barr virus infection (for nasopharyngeal cancers) are important risk factors for the development of head and neck cancers. Patient's presentation and clinical findings are occasionally nonspecific and can vary depending on the tumor location in the head and neck. Some of these cancers may escape detection despite detailed physical examination, endoscopy and conventional cross sectional imaging, and pose significant challenges in disease diagnosis and management. Imaging studies such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}F-2-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) are widely used to determine the presence and extent of tumors and metastatic disease, both before and after treatment. Advances in PET/CT imaging have allowed it to emerge as a superior imaging modality compared to both CT and MRI in select situations, such as detection of carcinoma of unknown primary (CUP), cervical lymph node metastasis, distant metastasis, residual/recurrent cancer and second primary tumors, often leading to alteration in management[2-5]. Furthermore, PET/CT as an imaging biomarker may provide an overall assessment of tumor aggressiveness with prognostic implications.

With PET/CT imaging, injected positron-emitting radionuclide ^{18}F-FDG is taken up by metabolically active cells, particularly cancers, in different concentrations depending on their relative metabolic rates. The radionuclide is initially transported into cells through glucose transporters with the same mechanism as for glucose but cannot be further metabolized. PET images are then created by detecting emissions from ^{18}F-FDG and reconstructed into a three-dimensional image. CT images are also generated sequentially and coregistered with PET images using fusion software, enabling functional data obtained on PET to be coupled with anatomical CT images. Quantification of FDG uptake is simplified by measurement of the standardized uptake value (SUV), which represents the activity of ^{18}F-FDG measured over a certain interval after radionuclide injection and normalized to its dose and the patient's body weight[6].
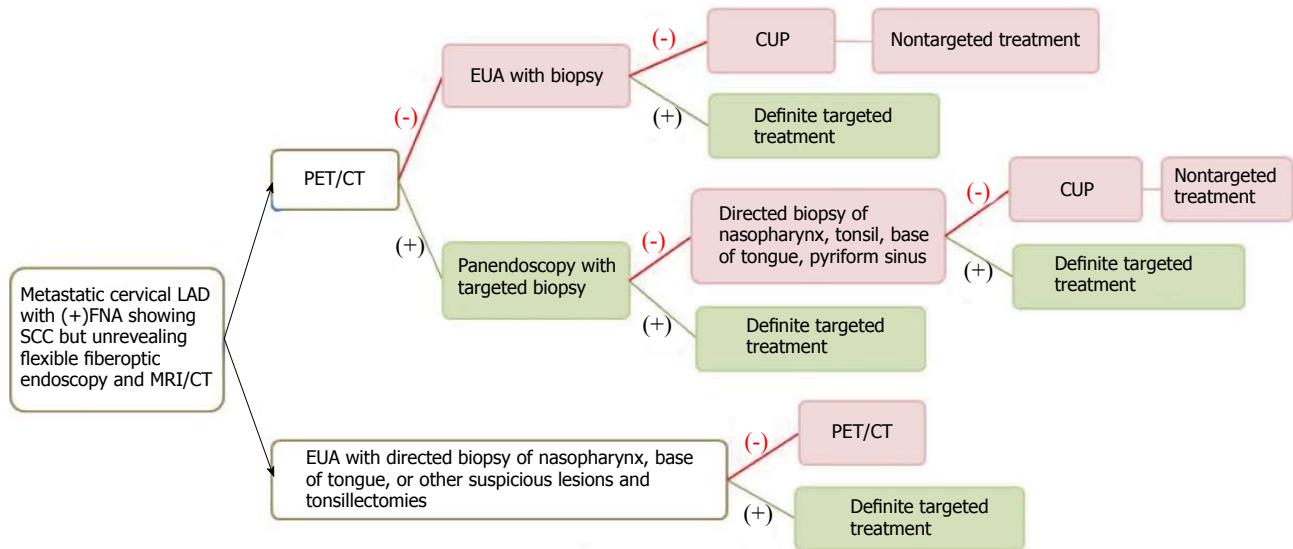
Since the implementation of PET/CT in head and neck oncology over a decade ago with its approval for reimbursement by the Centers for Medicare and Medicaid Services[7], PET/CT has provided high diagnostic accuracy. PET/CT remains especially valuable in detection of regional and distant metastases and evaluation of treatment response. As more patients are cured of their cancers, acute and long-term complications of multimodality approaches including surgery, radiation, and chemotherapy may alter the anatomy and physiology of the head and neck, posing significant challenge in assessing treatment response and detecting residual or recurrent tumor by clinical evaluation and conventional imaging techniques such as CT or MRI. PET/CT may prove helpful with treatment strategy in these patients as well as those with metastatic cervical lymphadenopathy of unknown primary site despite thorough workup.

As new developments emerged leading to better understanding and use of PET/CT in head and neck oncology, this article addresses the roles of PET/CT in both pre- and post-treatment management of HNSCC. PET-derived parameters as prognostic indicators are also discussed.

PRE-TREATMENT EVALUATION

Proper staging of the head and neck cancer, regional lymph nodes and detection of distant metastasis is critical for developing optimal treatment and determining prognosis. The tumor node metastasis (TNM) staging system of the American Joint Committee on Cancer, 7th edition is used to stage HNSCC[8]. The extent of the primary tumor (T stage) is site specific, while there is considerable overlap in classifying regional lymph node involvement (N0 to N3 stage) with the exception of thyroid and nasopharyngeal cancers. Metastasis outside head neck regions (*e.g.*, mediastinal and axillary lymph nodes) represents distant metastasis (M stage). Initial evaluation and staging include a combination of physical examination, imaging studies, and direct endoscopy with tissue biopsy or fine needle aspiration.

Imaging exams such as contrast-enhanced CT, MRI and PET/CT are important to assess the extent of local extension, involvement of lymph nodes, and presence of distant metastasis. Multiple studies suggest that PET/CT is superior to conventional imaging (CT or MRI) in initial staging and may alter management, especially when unexpected cervical lymph node or distant metastasis is discovered[2-5]. A multicenter prospective study found that PET/CT improved the TNM staging of the primary cancer

Figure 1 Algorithm in diagnosis and management of carcinoma of unknown primary. LAD: Lymphadenopathy; FNA: Fine-needle aspiration; SCC: Squamous cell carcinoma; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography; EUA: Examination under anesthesia; CUP: Carcinoma of unknown primary.

and subsequently altered the management in 13.7% of the patients, mainly due to the ability of PET/CT to detect metastatic or additional disease[9]. Furthermore, PET/CT can provide accurate tumor localization with precise metabolic tumor volumetric measurements, cervical lymph node staging, detection of metastases, and finding of synchronous second primary tumors that may alter radiation fields and doses for patients undergoing radiation therapy. The National Comprehensive Cancer Network issued an update in clinical practice guidelines in head and neck cancer and PET/CT imaging in 2013, recommending the use of PET/CT in initial staging of the oral cavity, oropharyngeal, hypopharyngeal, glottic, and supraglottic cancers for stage Ⅲ-Ⅳ disease as well as mucosal melanoma and nasopharyngeal carcinoma (World Health Organization class 2-3 and N2-3 diseases)[10].

The CT portion of the PET/CT examination provides the superior contrast and spatial resolution to detect malignant tumor using morphology (such as ill-defined, infiltrative, ulcerative features), enhancement, and interval growth. The PET portion demonstrates semiquantitative assessment with SUV of malignant tumor typically greater than 2.5-3.0[11]. Similarly, a maximum SUV greater than 2.5 is 100% sensitive and a maximum SUV greater than 5.5 is 100% specific for malignant lymphadenopathy[12]. However, SUV assessment should be used in conjunction with other clinical data given the overlap between a malignant lesion (high SUV) and a benign inflammatory uptake (low SUV).

Despite the proven efficacy of PET/CT, false negatives of PET/CT may be seen in patients with occult nodal metastases less than 5 mm or metastatic lymph nodes with necrosis[13-15]. Cancers with low metabolic activity or decreased FDG uptake may also limit PET/CT sensitivity. Therefore, PET/CT does not have the sensitivity to replace neck dissection and its usefulness is uncertain in evaluating patients with clinically negative (N0) neck[16]. In addition,
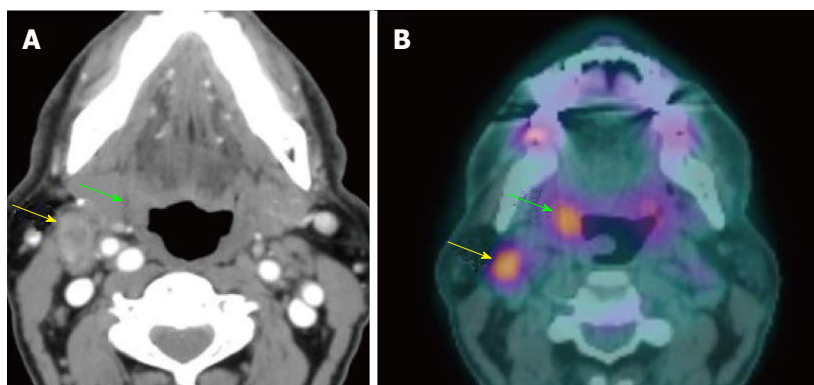
the utility of PET/CT in determining the resectability of head and neck cancers has not been fully explored to date; CT or MRI remains the mainstay in these patients[17].

Additional limitations unique to PET/CT include imaging artifacts, lower osseous and soft tissue contrast/resolution (when performed without intravenous contrast) as compared to contrast-enhanced CT and MRI, respectively. PET typically has a resolution of 5 mm[11], while unenhanced CT and MRI have submillimeter resolution[18]. The addition of intravenous contrast to CT and MR enhances visibility of the lesions and enable separation of the lesions from adjacent vessels. In this regard, contrast-enhanced CT and MRI are superior imaging modalities for evaluating T stage of HNSCC. There is currently no clear recommendation for routine use of PET/CT in initial T staging, as several studies demonstrated 5.5%-8.5% of patients had T staging upstaged on PET/CT[2,5].

CUP

Three to five percent of HNSCC patients present with metastatic cervical lymphadenopathy without definite primary site detected[2,19,20] despite a thorough history (often with nonspecific symptoms or no symptoms), combination of physical examination with office flexible fiberoptic endoscopy (for small submucosal lesion), or conventional contrast-enhanced CT/MRI performed. The work up algorithm to search for the primary tumor is shown in Figure 1, adapted from Tantiwongkosi *et al*[21] and Schmalbach *et al*[22].

The choice of treatment depends on staging and histology[23]. With locoregionally advanced cervical lymphadenopathy, the goal of treatment is generally directed at cure; whereas, cervical lymphadenopathy from unknown primary originating below the clavicles may represent incurable disease with distant metastasis. Failure to identify the primary tumor leads to nontargeted treatment (bilateral tonsillectomies, bilateral neck dissection, radiation to cover

Figure 2 Occult squamous cell carcinoma of the right palatine tonsil. The lesion (green arrow) was not appreciated on physical examination, flexible endoscopy and contrast-enhanced CT (A), but demonstrated hypermetabolic activity on PET/CT with maximal SUV: 3.5 (B). Biopsy directed by PET/CT revealed squamous cell carcinoma of the right palatine tonsil. The right level IIA lymphadenopathy also showed increased FDG uptake (yellow arrow). The patient remained disease free for 5 years after treatment. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value; FDG: 2-fluoro-2-deoxy-D-glucose.

the whole pharyngeal mucosa and neck)[24] resulting in increased complications, morbidity and mortality.

Several studies support the efficacy of PET/CT in detection of primary cancers in patients with CUP (Figure 2). PET/CT is able to identify the primary cancer in approximately 29% to 54% of cases (62%-93% sensitivity, 33%-93% specificity, 56%-89% positive predictive value and 25%-96% negative predictive value)[2,25-31]. A high detection rate of up to 54% can be achieved when the combination of CT, MRI, endoscopy under anesthesia and PET/CT are used. Generally, PET/CT is sensitive and superior for characterizing deep or metastatic cancers, while panendoscopy is more accurate for evaluating smaller or superficial mucosal lesions.

PET/CT is typically performed before panendoscopy to guide the selection of biopsy sites and to avoid erroneous interpretation due to high false positivity (as much as 50%)[29] of FDG uptake at sites manipulated during endoscopy. It is still uncertain when PET/CT should be performed after biopsy; therefore, if carcinoma of unknown primary is suspected, it is best to obtain PET/CT prior to endoscopy and biopsy/tonsillectomy. Over 90% of the unknown primary cancers are squamous cell carcinoma found in Waldeyer's ring (lymphoid tissue of the nasopharynx, palatine tonsils or base of tongue)[22,32]. Due to variable negative predictive value (25%-96%) of PET/CT, panendoscopy with directed biopsies and bilateral tonsillectomies are considered when PET/CT yields negative result[3]. Pattani *et al*[33] suggest careful selection of patients for panendoscopy after a negative PET/CT since primary cancer was only found in 9% of CUP cases (1 out of 11 patients).

Second primary malignancy

HNSCC patients are at increased risk for the development of second primary malignancy (SPM), with synchronous SPM occurring within 6 mo of the index primary cancer or metachronous SPM diagnosed > 6 mo of the index cancer. Approximately 1.4% to 18% of head neck cancer patients have SPMs[34], especially when the index cancers are laryngeal carcinomas. The risk for SPMs remains elevated for at least 10 years[35] and are mostly found in the head and neck, lung and esophagus[36] with the vast majority being squamous cell carcinoma[37]. Since SPM is the second leading cause of non-HNSCC death[38], early detection and
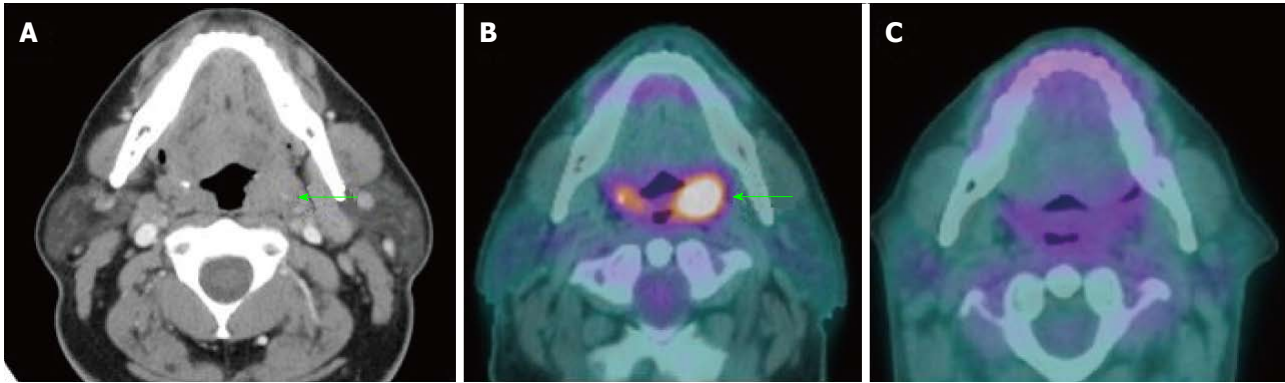
treatment of SPM may alter management and improve patient survival[34]. A meta-analysis revealed 87.5% sensitivity and 95% specificity of PET/CT in detection of SPM or distant metastasis, while a negative PET/CT study does not completely exclude the presence of SPM[39]. Given the low incidence of synchronous SPMs at initial evaluation of HNSCC patient, several research studies question the cost-effectiveness of panendoscopy[8]. Therefore, PET/CT may complement or replace panendoscopy in detecting synchronous SPMs. For patients with localized disease (stage I or II) being treated with either primary surgery or definitive chemoradiation therapy, a thorough physical examination combined with PET/CT may be adequate, obviating the need for panendoscopy unless tissue biopsy under general anesthesia is deemed necessary.

POST-TREATMENT EVALUATION

Therapy response assessment and residual tumor detection

Localized disease (stage I or II) comprising approximately 30% to 40% of HNSCC is generally treated with either primary surgery or definitive radiation therapy[40]. Loco-regionally advanced disease (stage III, IVA, or IVB) associated with high risk of local recurrence and distant metastasis requires a multidisciplinary approach, given the complexity and complications of combined treatment modality that includes surgery, radiation therapy and chemotherapy[41]. In select cases, radical concurrent chemoradiation can be used as a definite therapy in preference to surgery to achieve similar cure rates with preserved functional outcome and less morbidity[42].

For patients with locoregionally advanced disease who have undergone treatment, management of residual abnormalities can pose significant challenge. Both surgery and radiation may cause inflammation, fibrosis and distortion of the head and neck anatomy leading to difficulties of interpretation with conventional imaging, especially differentiating between residual cancer and complete response[43,44]. Inaccurate post-treatment assessment may result in delayed or unnecessary treatment and increased mortality and morbidity. In this regard, multiple studies have shown that PET/CT is superior to conventional anatomic imaging in assessment of tumor response and detection of residual tumor[3,45-47].

Figure 3 Complete treatment response at primary tumor site. Squamous cell carcinoma of the left palatine tonsil (arrows) was seen on contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 11.6. The tumor was no longer hypermetabolic on PET/CT with maximal SUV: 2.8 at 10 wk after treatment (C). PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

The sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT for detection of residual primary tumor have been reported as high as 94%, 82%, 75% and 95%, respectively[3]. It is important to note the very high negative predictive value of PET/CT: A negative study highly suggests absence of viable residual disease in both primary site and neck (Figures 3 and 4). The low positive predictive value is due to treatment-related FDG-avid inflammation or infection. A positive PET/CT study in the post-treatment phase needs careful correlation with clinical information and corresponding CT/MRI findings[48]. It is suggested that PET/CT should be performed no sooner than 2 mo after completion of treatment to evaluate for residual tumor while avoiding false positive results and to establish a baseline; however, it may be performed sooner if there is clinically suspected recurrent disease[49]. We generally recommend performing PET/CT around 3 mo after completion of treatment at our institution (Figure 5).

Long-term surveillance and recurrent tumor identification

Patients with complete treatment response, as documented clinically and by structural imaging (CT, MRI, and PET/CT), are generally observed. With advanced chemoradiation therapy, and improving surgical techniques, many patients may have distant metastasis as the first and only sign of treatment failure. PET/CT as a surveillance tool serves the purpose of detecting early recurrent disease, assessing for a metachronous second primary tumor, and excluding interval development of distant metastases. Close interval follow up in the first two to four years following treatment is necessary since 80% to 90% of all recurrences occur within this timeframe[50,51]; while the risk of SPM is higher than recurrence beyond three years[52,53].
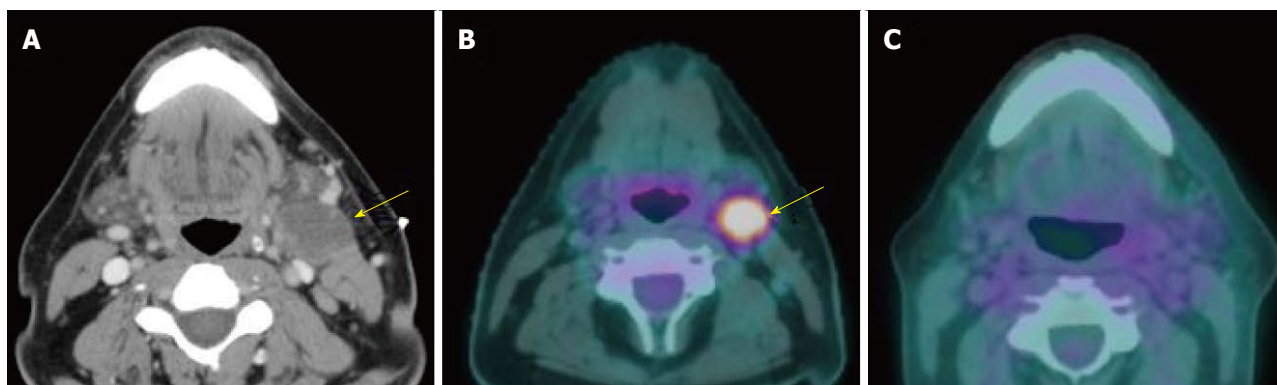
PET/CT has 93%-100% sensitivity and 63%-94% specificity in detection of recurrent tumor in both primary site and the neck, respectively[48,54,55] (Figure 6). The negative predictive value of a single PET/CT and double PET/CT (obtained within 6-mo period) are 91% and 98%, respectively. Negative results of two consecutive PET/CT studies could potentially eliminate the need for routine post-treatment imaging if there is no clinical suspicion of tumor recurrence[56]. In addition, there are no differences in survival between PET/CT detected and clinically detected recurrence[57]. Although there is an appreciable radiation dose and lifetime cancer risk associated with PET/CT, the use of this examination is warranted when utilized in the appropriate clinical setting[58].
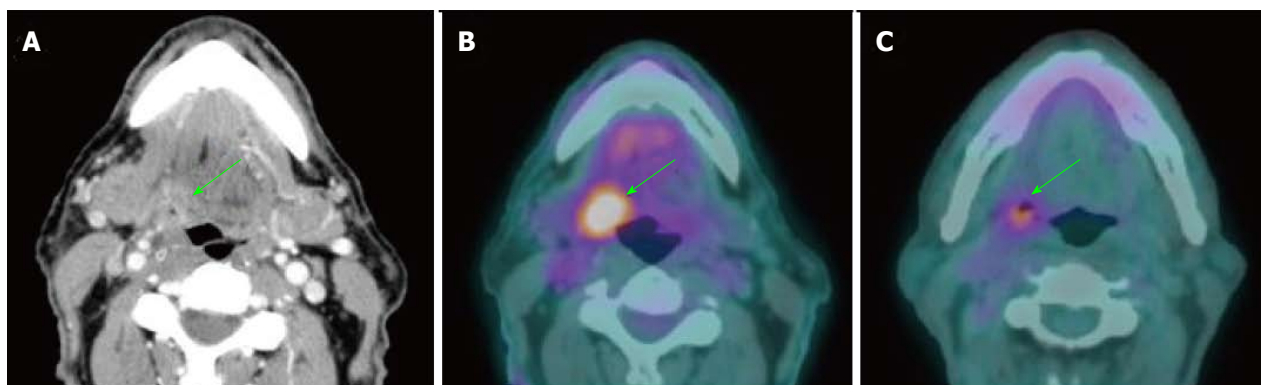
Metachronous second primary tumor may occur after 6 mo of the index primary tumor with 2.8% annual rate[59]. The incidence of distant metastasis following definitive treatment is 9% with the risk increased in patients with locally advanced stages[59,60] (Figure 7). Overall 17.9% of HNSCC patients develop second primary cancers or distant metastasis, especially in patients with recurrent disease[39,60]. The identification of distant metastatic lesions at the time of restaging recurrent tumors may obviate aggressive surgery while focusing on palliative chemoradiation options[60]. Therefore, PET/CT has strong utility in detecting second primary tumors or distant metastases with high sensitivity and specificity[39].

PROGNOSIS

As an invaluable tool in staging cancers of the head and neck, PET/CT imaging provides metabolic and functional data that may serve as quantifiable prognostic factors. The PET-derived parameters, SUV and its various forms, have been shown correlating well with glucose metabolism rate in various cancers, including HNSCC[61], and are useful in predicting tumor aggressiveness and long-term survival of patients[62]. They have also been used in selecting treatment modality and personalizing treatments. In a study comparing resectable, advanced HNSCC patients treated with surgery followed by chemoradiation therapy *vs* those with chemoradiation and salvage surgery, Roh *et al*[63] found that patients with high FDG uptake and treated with surgery first had better disease-free survival (DFS). In addition, Inokuchi *et al*[64] found that high FDG uptake

Figure 4 Complete response of metastatic cervical lymph node. Left level IIa metastatic lymphadenopathy (arrows) from the same patient in Figure 3 with squamous cell carcinoma of the left palatine tonsil was identified on both contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 12.1. After treatment, the lymph node was no longer hypermetabolic at 10-wk PET/CT (C) with maximal SUV: 2.5, representing complete response. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

Figure 5 Residual primary tumor. Squamous cell carcinoma of the right base of tongue (arrows) was identified on contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 10.2. The tumor remained FDG-avid on PET/CT (C) with maximal SUV: 4.8 at 12 wk after treatment, representing residual disease. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.
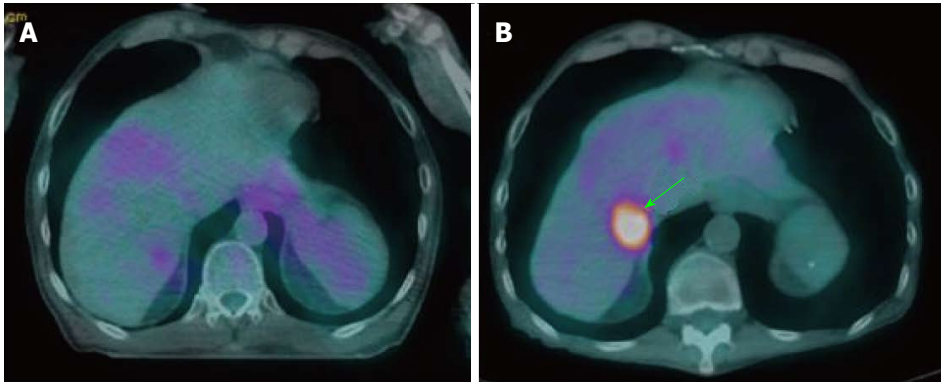

Figure 6 Recurrent primary tumor detected by positron-emission tomography/computed tomography. Squamous cell carcinoma of the base of tongue (green arrows) with bilateral level IIa metastatic lymphadenopathy (yellow arrows) was identified on pre-treatment PET/CT with maximal SUV: 13.2 (A). The tumor remained intensely hypermetabolic on PET/CT with maximal SUV: 6 at 13 mo after treatment (B). PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

in HNSCC patients treated with definitive chemoradiation predicted a decrease DFS, nodal progression-free survival, and distant metastasis-free survival. The investigators also suggested using pre-treatment FDG uptake of cervical lymph nodes to select patients for planned neck dissection. They found that patients with high FDG uptake and treated with planned neck dissection had better nodal progression-free survival.

Metabolic tumor volume (MTV), a SUV-based parameter representing the tumor volume that has SUV above a specific threshold, has been suggested in the literature as a robust measure in predicting treatment outcomes. For example, clinical trials are underway to explore if patients with human papillomavirus (HPV)-associated oropharyngeal cancers, which are known to have better prognosis than those not associated with HPV, would have similar cancer control with less intensified and therefore less toxic treatment options[65]. It has been suggested that this patient population could be stratified further based on MTV. Patients with more aggressive HPV-related HNSCC, as suggested

Figure 7 Failure of treatment due to distant metastasis. A: Pre-treatment PET/CT of the patient with squamous cell carcinoma of the base of tongue in Figure 6 did not reveal any increased FDG uptake in the liver; B: PET/CT performed at 13 mo after treatment showed new hepatic metastasis (arrow), representing treatment failure. PET/CT: Positron-emission tomography/computed tomography; FDG: 2-fluoro-2-deoxy-D-glucose.

by the increased MTV, had significantly poorer outcomes in one study conducted by Tang *et al*[66]. In addition to MTV, total lesion glycolysis (TLG) was first introduced by Larson *et al*[67]. It is the product of mean SUV and MTV, combining the volumetric and metabolic information of PET/CT to evaluate treatment response. Recent studies demonstrate the usefulness of TLG for evaluating head and neck cancers, with high TLG correlating to increased risk of adverse events or death[62,68,69].

The PET-derived parameters are also currently used in combination with other prognostic factors. N-stage, T-stage, and pre-treatment SUV of lymph node when used in combination have been shown better at predicting distant metastasis-free survival than individual factors[70]. Recently, there has been increased interest in identifying prognostic molecular biomarkers. Moeller *et al*[71] incorporated HPV status in addition to post-treatment FDG uptake in their mortality risk assessment. In addition conventional parameters (SUV, MTV, TLG, tumor volume, and diameter) in PET/CT, textural parameters to assess tumor heterogeneity such as coefficient of variation, skewness, and kurtosis may also provide prognostic information but are not fully explored in head and neck oncology.

CONCLUSION

With wide-spread availability and use, PET/CT imaging maintains an important role in head and neck oncology. In the pre-treatment phase, PET/CT is valuable in the evaluation of patients with carcinoma of unknown primary origin before panendoscopy and biopsy, detection of synchronous second primary tumor, staging of cervical lymph node metastasis and assessment for distant metastases. In the post-treatment phase, PET/CT is helpful in evaluating treatment response, detecting residual or recurrent tumor and excluding distant metastases. Prognostic factors derived from PET/CT metabolic and functional data are useful in predicting tumor aggressiveness with implication on patient's survivability, and facilitate selection of treatment modality and personalized treatment options.

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