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Name of journal: World Journal of Otorhinolaryngology
ESPS manuscript NO: 22308
Title: PET/CT Imaging in Head and Neck Oncologic Surgery: An Update

Reviewer's code: 00503898
Comments to authors
Comments to Authors - manuscript: 22308 Title: "PET/CT Imaging in Head and Neck Oncologic Surgery: An Update". The authors have provided an excellent and detailed manuscript on the role of PET-CT in head and neck cancer. However, after careful consideration of the manuscript, I think that there is a weak point: 1. Title: I suggest the authors to modify the title to PET/CT Imaging in Head and Neck Cancer Patients: An Update".

RESPONSE:
We have modified to the title to: "PET/CT Imaging in Head and Neck Oncology: An Update"

Reviewer's code: 00667415
Comments to authors
RE: PET/CT imaging in Head and Neck Oncologic Surgery: An Update The authors summarized the current practice and application of PET/CT in the management of head and neck cancer, highlighting the strength and weakness of PET/CT. I think this review is helpful for readers, particularly clinicians responsible for managing head and neck cancer patients. I made a few suggestions to improve it. 1) Title: I don't understand the reason why the authors used the term 'surgery', cause the paper dealt with all fields of head and neck cancer management through PET/CT application. I recommend the correction of title, PET/CT imaging in Head and Neck Oncology, instead of Oncologic Surgery. 2) Pre-treatment evaluation 2nd paragraph, 9th line. with precise tumor volumetric measurements should be changed to with precise metabolic tumor volumetric measurements. 3) Pre-treatment evaluation 3rd paragraph, 3rd sentence. Additional limitations unique to PET/CT include imaging artifacts, lower osseous and soft tissue contrast/resolution as compared to CT and MRI, respectively. Add more explanations and insert relevant references cited. 4) Long-term surveillance and recurrent tumor identification 1st paragraph, 3rd sentence. Close interval follow-up in the first tow --, while the risk of SPM is higher than recurrence beyond three

years. Insert references cited. 5) Prognosis After MTV paragraph, add some explanations about the concept of total lesion glycolsis and PET heterogeneity, which has been tried in the metabolic measurements of cancer tissues.

RESPONSE:

1) We have modified to the title to: "PET/CT Imaging in Head and Neck Oncology: An Update".
2) 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.
3) 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[1, 4].
4) 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].
5) In addition to MTV, total lesion glycolysis (TLG) was first introduced by Larson and colleagues[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].

   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 [COV], skewness, and kurtosis) may also provide prognostic information but are not fully explored in head and neck oncology.

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Reviewer's code: 00503711

Comments to authors

Good review presenting up-to-date and concise information on the utility of PET in HNSCC. There are a few clarifications that I have sought- Title would be better with head and neck oncology rather than oncologic surgery Introduction - 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" - would be better Intro- para 3 - line 4 - "regional" -not local More info on comparison of PET with CT/MRI on regional staging would be useful i.e., data on ability to identify extracapsular spread, assess resectability based on relationship to carotid, prevertebral muscle. What is the role of PET in cases that have undergone thorough physical exam and CT/MRI and staged clinically as early stage (T1-2 N0) disease ? Is there any data on PET upstaging these tumors? Figure 4 - mentioned right instead of left node Is there any data to support routine use of PET 6 months after curative treatment in order to detect occult recurrent/metastatic disease ?

RESPONSE:

1) We have modified to the title to: "PET/CT Imaging in Head and Neck Oncology: An Update".
2) 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[1-4].
3) PET/CT remains especially valuable in detection of regional and distant metastases and evaluation of treatment response. 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 MR imaging remains the mainstay in these patients[17].
4) 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[1, 4].

5) 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 A) contrast-enhanced CT and B) pre-treatment PET/CT with maximal SUV: 12.1. After treatment, the lymph node was no longer hypermetabolic at C) 10-week PET/CT with maximal SUV: 2.5, representing complete response.
6) It is suggested that PET/CT should be performed no sooner than 2 months 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 months after completion of treatment at our institution (错误!未找到引用源。).

Reviewer's code: 02517857

Comments to authors

This manuscript is a well written review article concerning PET/CT on head and neck cancer (most of the part is written for HNSCC). However, I am wondering that how do the radiologists determine the abnormal view from PET/CT as malignant-tumor related lesion? They might have their own criteria for diagnosis, probably by the structural abnormality from CT and SUV from PET. Especially in the pre-treatment evaluation part, I am very interested in a cut-off value of SUV to discriminate metastasized lymph nodes from non-metastasized lymph nodes. (Minor points) 1. PPV and NPV should be full-spelled. 2. Followup should be "follow up".

RESPONSE:

1) 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).

2) We have modified the manuscript according to the reviewer's minor points.