Review Article, PET/CT.

^{18}F-FDG PET/CT Prognostic Parameters in Patients with Head and Neck Cancer.

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ABSTRACT:

In head and neck cancer, computed tomography (CT) magnetic resonance (MR) imaging are routinely used. However 18F FDG PET-CT has been shown to have higher sensitivity and a high negative predictive value for identification of small lymph nodes of the neck especially using the volume of ^{18}F-FDG - avid disease (MTV) and the total lesion glycolysis (TLG) as a prognostic indicator. Metastasis in HNSCC is relatively low and it implies a poor prognosis and has a major impact on patient management. Additionally, patients with HNSCC have a higher prevalence of synchronous and metachronous primary tumors, which can be detected at FDG PET/CT. ^{18}F-FDG PET is the most sensitive noninvasive modality presently available for differentiating post-treatment changes regardless of the primary treatment modality used from residual or recurrent disease as compared to CT and MR. PET-CT hypoxic imaging is a growing diagnostic modality as Hypoxia represents a negative prognostic factor for radiation treatment where it is associated with a significant resistance to radio-chemotherapy. Several PET tracers have emerged for this purpose like (^{18}F-FMISO), (^{18}F-FAZA). Radiomics as an emerging technology concerned with extraction of numerous quantitative parameters by extraction features from different imaging modalities (CT, MRI, and PET-CT). Radiomics commonly describe shape; intensity and texture characterization and it provide fast, cost-effective non-invasive comprehensive tissue characterization that offer complementary information to conventional clinical and imaging modalities.

Key Words: PET/CT & Head and Neck Cancer & Metabolic Parameters.

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INTRODUCTION:

Head and neck tumors are not considered as a specific entity, but rather a broad spectrum of diverse tumor types arising from different anatomical origin including the craniofacial bones, soft tissues, salivary glands, skin, and mucosal membranes. Squamous cell carcinoma (SCC) is the most common pathology in head and neck tumors. Responses to clinical treatments vary greatly among HNSCC patients and remain challenging and considering the significant toxicity as a result of chemotherapy and radiation therapy, it is therefore crucial to identify biomarkers with which to select the best treatment strategy for each patient [(1)]. Conventional imaging modalities can't significantly predict tumor aggressiveness and hence failure to attainment of complete remission is the major quest in treating this category of tumors. The emergence of a cost effective, non-invasive technique is now possible with the introduction of Radiomics as it has the potential to enable quantitative measurement of tumor heterogeneity and offering the possibility of treatment monitoring and optimization [(2)].

^{18}F-FDG PET-CT in head and neck squamous cell carcinoma: In head and neck cancer, computed tomography (CT) magnetic resonance (MR) imaging is routinely used. However 18F FDG PET-CT has been shown to have higher sensitivity and a high negative predictive value (compared to CT or MRI) especially for identification of small lymph nodes of the neck [(3)]. Furthermore, in patients with cancer of unknown primary manifested with cervical lymph node metastases, FDG PET can identify the primary site in 25 –38.5% of cases [(4)].

Initial PET-CT in HNSCC: For optimal therapeutic approach, accurate delineation of the primary tumor, the extent of regional lymph node metastases as well as metastases detection is critical for staging of the tumor. Numerous reports have shown that PET is at least as sensitive as MRI or CT in detecting the primary tumor Lymph node involvement is the most important prognostic factor, as survival is found to decrease by 40-50 % in patients with positive nodal involvement, studies showed that 18F-FDG PET/CT is comparable or superior to conventional imaging in detecting regional lymph node metastases during initial staging [(5)].

A meta-analysis encompassing 32 studies and 1236 patients that evaluated the performance of FDG PET in lymph nodes staging showed an overall sensitivity of 82% and specificity of 86% for FDG PET and an approximate 5–10% improvement in both performance values compared with CT, MRI, or both CT and MRI [6].

Metastasis in HNSCC is relatively low (2–18%) and it implies a poor prognosis and has a major impact on patient management. Additionally, patients with HNSCC have a higher prevalence of synchronous and metachronous primary tumors, which can be detected at FDG PET/CT. The National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of FDG PET/CT in the assessment of the initial treatment strategy for advanced stage (III, IV) oral cavity, pharynx, and larynx cancers; nasopharyngeal cancer; head and neck cancers of an unknown primary [7].

Cervical nodal metastases of unknown primary:

They accounts for about 1- 2 % of the diagnosed head and neck cancers. An early meta-analysis by ***Rusthoven et al***. where 16 studies were done with total of 302 patients. PET/CT showed an added detection rate of 25% compared to other conventional imaging [7].

Zhu et al. reported in a meta-analysis of total 7 studies including 246 patients, a sensitivity of 97% and specificity of 68% for the detection of primary sites in patients with cervical nodal metastases of unknown origin by FDG-PET-CT [8]. ***Roh et al***. compared the performance of combined ^{18}F-FDG PET/CT and diagnostic CT alone in 44 patients with cervical MUO. 18F-FDG PET/CT was reported to be more sensitive than CT (94.0% versus 71.6) but with same specificity for both modalities [9].

Prognostic value of initial PET-CT:

PET-CT can assess the aggressiveness and proliferation rate of HNSCC, the intensity of FDG uptake at the primary site or neck node metastases correlates with prognosis in patients both with primary and recurrent disease. The volume of ^{18}F-FDG avid disease (MTV) and the total lesion glycolysis (TLG) have also been suggested as a prognostic indicator. Although high ^{18}F-FDG uptake and a large MTV thus indicate a poor prognosis, still no cut-off values have been established [7]. ***Minn et al***. Reviewed results from 37 patients with HNSCC. SUV cutoff of 9.0 was suggested and the results shows (3-year disease-free survival (DFS) was 53% for patients with SUV <9.0 compared with a 3-year DFS of 24% for patients with SUV >9.0) [10].

Another study by ***Machtay et al***. analyzed the baseline SUV in a retrospective study of 60 HNSCC patients found that the 2-years DFS rates were 76% in patients with SUV max <9.0 versus 37% in those with SUV max ≥9.0 (p = 0.007), both studies suggest that SUV max can be a valuable biomarker for predicting tumor aggressiveness [(11)].

A retrospective study in determination of prognostic values of the initial quantitative and visual parameters included 108 patients with head and neck cancer where initial and post therapy FDG PET/CT was done. It was reported that SUV max (> 10 g/mL) of the primary tumor, MTV (> 20 cm), TLG (> 70 g), and uptake pattern (ring-shaped) were significantly associated with worse disease-specific survival (DSS) and disease-free survival (DFS), uptake pattern remained significantly associated with DSS (p < 0.001), whereas the association between DSS and MTV was not significant [(12)].

Association between preoperative FDG-PET/CT parameters and outcomes among patients with HNSCC was reviewed by 36 studies which comprised 3585 patients with a median follow-up of 30.6 months.

32 studies showed an association between at least one FDG-PET/CT parameter and oncological outcomes (OS, DFS, and DM). The FDG-PET/CT volumetric parameters [MTV] and [TLG] were independent prognostic factors and showed higher prognostic value than the (SUV max). By analyzing OS, it was correlated with SUV max in 5 of 11 studies, with MTV in 11 of 12 studies and with TLG in 6 of 9 studies [(13)].

PET-CT in monitoring treatment response: FDG-PET-CT has a valuable role in detecting treatment response and in assessment of residual tumor viability in organ preserving therapy due to limitation of the conventional imaging modalities in identifying viability post-therapy [(14)].

Hentschel et al, conducted a prospective study from 2005 to 2009 included 43 patients receiving CRT. Initial and interim PET-CT was done for the purpose of prediction early treatment response with median follow up of 26 months analysis of (SUV max), (SUV mean) with correspondence of (OS), (DFS) and loco regional control (LRC). The 2-year OS (88%) and 2-year LRC (88%) were higher for patients who showed decrease of the SUV max 50% or more after treatment than for patients with Δ SUV max < 50% (2-year OS = 38%; p = 0.02; 2-year LRC 40%; p = 0.06) [(15)].

Malone et al, conducted a retrospective analysis with a median follow-up of 24 months to assess the role of PET-CT in early CRT treatment response prediction. 31 patients underwent PET-CT 6 to 8 weeks after the completion of treatment. Patients with positive residual findings by physical examination, CT, or PET-CT underwent surgical intervention while those with a complete clinical response were kept follow-up. Post-therapy assessment by PET-CT showed sensitivity, specificity, and positive and negative predictive values of 83%, 54%, 31%, and 92%, respectively. In patients with loco-regional nodal metastases, the sensitivity, specificity, and positive and negative predictive values of post-therapy PET-CT were 75%, 94%, 75%, and 94%, respectively while for N0 the specificity and negative predictive value for were 92% and 92%, respectively. This study suggests that negative PET-CT findings can accurately determine early disease response and patients with a negative PET-CT finding may not require further surgical intervention [(16)].

Sherriff et al. Conduced a retrospective study in a 9 year period for 92 patients whom received radical CRT. Post-therapy PET-CT was done in median time of 3 (range 2-8) months and median follow-up was 19 and 25 months. For local recurrence, the negative predictive value was 91.8%. The median SUV max values were 10.2 in those with local recurrence and 6.89 in absence of local recurrence. It was suggested that negative post-therapy PET/CT can be associated with 91.8% chance of remaining free of local recurrence 19 months post-treatment while high SUV max value on the post-therapy PET/CT may predict subsequent local recurrence and warrants further investigation [(17)].

Gupta et al, Conducted a systematic review and meta-analysis of studies assessing the diagnostic performance of FDG PET with or without CT in post-treatment response assessment. A total of 51 studies involving 2,335 patients were included and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were extracted.

The mean pooled sensitivity, specificity, PPV and NPV was 79.9%, 87.5%, 58.6% and 95.1% respectively with scan done ≥ 12 weeks after end of treatment showed higher diagnostic accuracy. It was concluded that post-therapy PET-CT has sub-optimal PPV with exceptionally high NPV and thus a negative post-treatment scan is highly suggestive of absence of viable disease and regular follow up is advised [(18)].

Detection of recurrence: Post-treatment fibrosis, tissue edema, and anatomical distortion can limit the use of conventional imaging modalities. A survey of the literature showed that ^{18}F-FDG PET is the most sensitive noninvasive modality presently available for differentiating post-treatment changes regardless of the primary treatment modality used from residual or recurrent disease and that its performance is higher compared CT and MR for this purpose.

In a retrospective study of 143 patients with HNSCC, including 72 patients in whom recurrent disease was ultimately proven, Wong et al. found a sensitivity of 96% for ^{18}FDG PET **(19)**.

For the detection of residual primary HNSCC, a large meta-analysis of 51 studies involving 2335 patients and sensitivity, specificity, (PPV), and NPV of PET/CT were reported to be 94%, 82%, 75%, and 95%, respectively **(18)**.

Non FDG PET tracers in head and neck cancer: PET-CT hypoxic imaging is a growing diagnostic modality. Hypoxia represents a negative prognostic factor for radiation treatment where it is associated with a significant resistance to radio-chemotherapy. Several PET tracers have emerged for this purpose like (^{18}F-FMISO), (^{18}F-FAZA) **(20)**.

The proliferation marker 18F-FLT is been now investigated as a possible predictor to therapy response. The proliferation marker (^{18}F-FLT) was investigated by de ***Langen et al***. in 6 patients with HNSCC to evaluate the reproducibility of quantitative ^{18}F-FLT measurements. Quantitative measurements were reproducible for predicting response to therapy **(21)**. A prospective study on 13 patients were they underwent initial ^{18}F-FDG PET/CT with sensitivity, specificity, and accuracy at initial staging were (89%, 50%, and 81%) while for ^{18}F-FET PET/CT, (70%, 90%, and 74%). Follow up showed sensitivity, specificity, and accuracy for ^{18}F-FDG PET/CT (71%, 65%, and 67%) and (29%, 100%, and 83%) for ^{18}F-FET PET/CT.

^{18}F-FDG PET/CT also detected a higher number of double primaries or distant metastases. FET-PET-CT scan shows more specificity but less sensitivity than FDG-PET-CT and can't be used as a substitute **(22)**.

Radiomics: Morphological variation between different regions of a tumor, cellular density difference, proliferation, necrosis, fibrosis, metabolism, hypoxia, angiogenesis and receptor expression, and these factor independently associated with poor treatment response and more aggressive tumor behavior, however only the high grade pathological features are reported, thereby additional quantitative PET/CT data extraction, analysis and interpretation should be tumor characterization as it will facilitate treatment prediction or prognostication, to an extent that allows treatment personalization [(23)].

Radiomics as an emerging technology concerned with extraction of numerous quantitative parameters by looking beyond the digital medical images, then correlating these bio-image based information with either an outcome to create a new biomarker or correlating them with a gene expression profile and hence it will be called Radio genomics. By extraction features from different imaging modalities (CT, MRI, PET-CT), radiomics commonly describe shape, intensity and texture characterization and it's proved to provide fast, cost-effective and mostly non-invasive comprehensive tissue characterization that offer complementary information to conventional clinical and imaging modalities that could help advance cancer care towards personalized standard of care [(24)].

Radiomics emphasis images acquisition of high quality, preferably standardized images followed by reconstruction. Tumor segmentation of the target area/volume referred as region of interest (ROI) or volume of interest (VOI) is considered the main core of the workflow, it's done either manually or automated. Although manual segmentation is operator dependent and can harbor some variability especially in tumors with indistinct borders, it provides fair level of quality that can be missed by the automated method [(25)].

Features extraction is the most valuable step for analysis and correlation. Two types of features can be extracted, semantic, a descriptive lesioned analysis (size, shape,…) and agnostic, a mathematical data consistent with tumor heterogeneity. Agnostic data are subdivided into first, second and higher order output. First order output are consistent with reduction of the region of interest into simple values as mean, median, maximum, minimum, and uniformity or randomness (entropy), skewness (asymmetry) and kurtosis (flatness) of the values, it corresponds to quantitative PET-CT (SUV max and SUV mean).

Second order output used to describe textural heterogeneity with the tumor by defining the similar pixels or voxels of the tumor. High order data implies applying a filter grids for extraction of data with repetitive or with non-repetitive pattern [25, 26].

Specific applications for texture analysis and radiomics in HNSCCs have been applied in tumor segmentation and pathological classification of inter-tumor heterogeneity that can guide the site of biopsy or resection, risk stratification and as a prognostic and/or predictive biomarkers and last but not least in monitoring pathological changes in normal tissues post-radiotherapy [27].

A study conducted by ***Yu et al***. on 40 patients with HNSCCS found that the neighborhood gray-tone difference matrix (NGTDM) features can significantly have a discriminatory role between normal and abnormal ROIs [28].

Zhang et al. analyzed the predictive value of texture and histogram features in 72 HNSCC patients they found that primary mass entropy and histogram skewness can also serve as predictive values beside the known factors as tumor volume and N stage [29].

A large study involving 1019 patients of lung and head and neck cancer, 440 radiomics features were extracted on CT images and classified into 4 groups describing tumor, shape and texture. By applying these features they showed statistical significance in both lung and head and neck subsets [30].

Bogowicz et al. Conducted a study on 121 patients with HNSCC feature were extracted from both CECT and FGD PET indicated homogenous tumor has better prognosis. However prognostic value of CT show more overestimation than PET CT which is recommended for initial prognostication [31].

CONCLUSIONS:

PET-CT can assess the aggressiveness and proliferation rate of HNSCC, the intensity of FDG uptake at the primary site or neck node metastases correlates with prognosis in patients both with primary and recurrent disease. Radiomics as it has the potential to enable quantitative measurement of intra and inter tumoral heterogeneity and offering the possibility of longitudinal use in treatment monitoring and optimization.

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