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Role of Pre -Treatment FDG PET Quantitative Parameters in Prognostication of Head and Neck Squamous Cell Carcinoma - A Review

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Abstract

In spite of the good organ preservation strategies available for locally advanced Head and Neck Squamous Cell Carcinoma (HNSCC), failure rates have been reported to be as high as 35-50%. There has been an increasing interest in predicting response to treatment, to aid early intervention and better outcomes. FDG-PET is a standard modality for post treatment evaluation, however it is still under utilized as a pre-treatment investigative modality. Several articles have described quantitative parameters in pre-treatment FDG-PET to prognosticate patients and determine likelihood of response to treatment however they are still not used commonly. This article was a review of the literature available on pre-treatment FDG PET quantitative parameters and their value in predicting failure. A thorough review of literature from MEDLINE and EMBASE was performed on pre-treatment quantitative parameters in HNSCC. Metabolic Tumor Volume (MTV) and Total Lesion Glycolysis (TLG) were reliable parameters to predict response to organ preservation therapy, disease free and overall survival. SUVmax was an inconsistent parameter. MTV and TLG may help predict poor response to organ preservation to initiate early surgical salvage or modify therapeutic decisions to optimize clinical outcomes. Routine incorporation into PET reporting may provide additional information over SUVmax alone.

Introduction

Locally advanced Head and Neck Squamous Cell Carcinoma (HNSCC) radical treatment options are most often radiation therapy with concurrent chemotherapy or surgery, depending on subsite, patient's performance status, co-morbidities and choice. Particularly in larynx, hypopharynx and oropharynx, organ preservation protocols have been popularized which use a combination of radiotherapy with chemotherapy and/or biological agents [1] because of improved clinical outcomes when compared to the use of radiotherapy alone [2]; however loco regional failure rates have been reported to be as high as 30-50% [3] and these multimodal approaches are also associated with significant short and long-term morbidity [4]. As a result there has been an increasing interest in predicting response to treatment - factors that predict a poor response to treatment and early identification of a suboptimal therapeutic response would be valuable in ceasing or intensifying ineffective treatment early on, reducing the associated morbidity and if possible, increasing the chance of cure. In organ preservation protocols, studies reflect that post therapy FDG PET scans performed before 12 weeks have lower negative predictive value for detecting residual disease [5]; hence to avoid this delay in detecting non-responders, there has been interest in predicting therapeutic response from pre-treatment or early-treatment FDG PET scans [6,7].

Clinical and Research Consequences

Factors determining prognosis in advanced HNSCC

The important clinical factors that determine prognosis of HNSCC include age and performance status, subsite and tumourstage [8]. For laryngo-hypopharyngeal cancers, the major determinants for staging the tumour are vocal cord fixity, extra-laryngeal spread and cartilage invasion [9]; CT may have difficulties in determining these in advanced tumours and MRI tends to over-stage the tumor in the presence of inflammation leading to poor specificity [10-13]. FDG PET scans provide direct information on tumor metabolism; malignant tissues have been demonstrated to selectively up-regulate glucose transporters glut-1 and glut-3, and hexokinase activity, leading to increased glycolysis, the degree of which may be linked directly to the clinical behavior of the tumor [14,15]. Analysis of the uptake of 2-[^{18}F] Fluoro-2 Deoxy-D-Glucose (FDG) yields several parameters that yield clinical information, such as standardized uptake value, metabolic rate, inverse coefficient of variation, and others.

Influence of factors determining prognosis on management

The importance of pre-treatment prognostic indices seems to be in prediction of disease free survival and/or loco-regional control, depending on which index is used [16-18]. By identifying tumors that are less likely to be loco-regionally controlled, early discontinuation of suboptimal treatment may confer better outcomes. Additionally, post chemo radiation FDG PET scans have a high negative predictive value (up to 95%) but considerably lower specificity and positive predictive value; hence an unequivocal response to treatment can be a considerable challenge [19]. Identifying patients likely to have loco-regional failure may also lower the threshold for salvage surgery in these patients.

Integrating PET use into routine management of head and neck squamous cell carcinoma

The role of FDG PET in HNSCC has been established in a post-treatment setting after organ preservation therapy [20-22] in a setting of locoregionally advanced [23,24], metastasis of unknown origin [25], for a detection of second primary tumours or recurrent disease [26]. Although pre-treatment FDG PET has shown increased sensitivity and specificity in staging HNSCC compared to conventional cross-sectional imaging, the reasons for its limited utilization in this setting may be its cost, poor anatomical resolution and availability [27]. However additional prognostic information conveyed by the use of FDG PET may favour its use in certain clinical settings.

PET Quantitative Parameters

Maximum standardized uptake value (SUV_{max})

Maximum standardized uptake value (SUV_{max}) is the most common parameter used to estimate metabolic activity in FDG PET CT, based on the principle that malignant cells have increased FDG uptake compared to the surrounding tissue [28]; it has been shown to correlate with metabolic activity, proliferation and in some instances even prognosis [29]. SUV is calculated by the expression $SUV=r/(a'/w)$, where r is radioactivity concentration in kBq/ml measured by the PET scanner within the region of interest, a' is the decay-corrected quantity of intravenous radiolabelled FDG tracer and w is the weight of the patient in grams, which acts as a surrogate for total volume of distribution for the tracer. Hence, it is assumed that if the 18 FDG is distributed evenly throughout the body, that the SUV will be 1. The SUV_{max} refers to the maximum SUV in the region of interest.

In head and neck cancers specifically, the role of SUV_{max} has been studied extensively. Schwartz et al [30] showed that HNSCC patients undergoing definitive radiotherapy (including post-operative adjuvant radiation) with or without chemotherapy with a pre-treatment SUV_{max} of greater than 9 had poorer local control and disease free survival. Torizuka et al. [31] showed pre-treatment SUV_{max} over 7 was associated with worse 2-year local control rates and disease free survival. Similar data showed a general prognostic trend but were not potentially practice-altering; subsequent studies were focused on identifying response to treatment to predict candidates whose treatment was likely to fail, in order to escalate or change the treatment modality. This was demonstrated by altering the timing of FDG PET CT evaluation.

Brun et al. [32] performed 2 FDG PET CTs, one pre-treatment and the second on average after delivery of 24Gy and compared the two. There was a statistically significant difference between complete remission, overall survival and locoregional control rate between the low and high values of metabolic rate and SUV_{max}. They noted that metabolic rate was a superior index compared to SUV_{max}. These results, however, were not universal. Castaldi et al [33] performed pre-treatment, post 2–week treatment (early) and post 8-12 week treatment (late) PET CTs. They found no correlation with pre-treatment or post 2-week treatment value, but post 8-12 week treatment ('late') scans with SUV_{max} over 8.7 were associated with lower rates of recurrence free survival, disease specific survival. Hentschel et al. [34] performed FDG PET CT post 1 or 2 weeks treatment, showing that a fall in SUV_{max} by 50% or more from the baseline was associated with improved locoregional control rates.

Cumulative data showed SUV_{max} was a more complex parameter of tumor activity than initially thought; rather than an isolated prognostic factor, clinical implications were stronger when using it serially as a surrogate marker for an alteration the metabolic activity of the tumor based on the response to treatment. Furthermore, these inconsistencies fueled the search for a more robust, reliable FDG PET CT parameter to predict tumor response.

Factors affecting SUV

The factors affecting standardized uptake value are broadly divided into biological factors, technological factors and local factors [35]. Some of the biological factors include body weight and composition, body surface area and respiratory movement; the first two may be especially relevant in a patient on chemo radiation who may have significant weight loss. Technical factors have been eliminated to some extent by standardizing protocols, but it is recommended that serial PET evaluation is performed in the same centre by the same machine, with the same dosage of FDG and the same interval between injection and imaging to minimize variability. Local factors may be especially relevant in a post-treatment setting –inflammation can mimic malignancy, especially in a post-radiotherapy setting, producing an over-estimation of tumor size or a false positive result.

Inconsistencies in using SUV as a parameter

The aforementioned factors may be the reason for the inconsistent performance of SUV. Hence newer parameters were studied and several showed a more durable response when compared to SUV_{max}. Higgins et al. [36] showed in their study on 88 patients of primarily oropharyngeal and laryngeal SCC that pre-treatment FDG PET CT derived SUV_{mean} was associated with a decreased disease free survival ($p=0.01$). They found no statistical significance between pre-treatment SUV_{max} and total lesion glycolysis (TLG) and patient outcomes. A study by Schinagl et al. [37] showed PET_{VIS} (a visual interpretation parameter from the PET) and GTV_{CT} (tumour volume as determined by CT) were the only parameters that could predict disease free survival, distant metastasis-free survival and overall survival; SUV_{mean} and SUV_{max} could not. Their literature review further showed that out of a total of 15 studies that used SUV_{max} as to predict treatment outcome, only 8 could establish a statistically significant relationship [38-45] whereas 7 could not [46-52]. The reasons for this, besides those mentioned earlier, include considerable heterogeneity in treatment modalities, use of several varied endpoints and the difference between SUV_{max} of the primary tumour and the lymph nodal metastases. Of the 8 studies that showed statistical significance, 55% of the patients (227 patients) underwent primary surgery as treatment modality. From

the existing data, the only definitive conclusion that can be drawn is that SUV_{max} is still unsubstantiated as a standalone parameter that can predict treatment response, either as a single value, or even serially.

Metabolic tumor volume

Metabolic Tumor Volume (MTV) is a fairly novel parameter, defined as the volume of tumor tissue that shows increased FDG uptake, and represents both metabolic activity and 3D volumetric data, unlike SUV_{max}. MTV is considered a more accurate marker of tumor metabolic activity. MTV is defined as the hypermetabolic tissue within the region of interest that has an SUV of 2.5 or more. Although T staging for larynx does not strictly include size of the tumor, there have been studies showing that tumour volume determined by imaging has prognostic value [53], making MTV an interesting tool to determine prognostication of HNSCC treated by chemo radiation. Hence MTV was evaluated as a prognostic indicator by predicting locoregional control rates and recurrence rates, overall and disease free survival in pre and post treatment settings.

Chung et al. [54] published once of the first studies on role of metabolic tumor volume in predicting response to radiotherapy or chemo radiation in pharyngeal cancer. Their retrospective study was to determine role of pre-treatment FDG PET derived MTV values in 82 patients in predicting short outcome and disease free survival. Their study demonstrated that with an MTV of >40ml, there was a significantly lower chance of complete response (using RECIST criteria) or no recurrence. In a multivariate analysis, these patients also had a significantly lower disease free survival. They found no correlation with outcomes and SUV. Interestingly, they were also able to derive a correlation between range of MTV and each clinical T stage and N stage. The range of MTV for each clinical T stage was wide (or example cT_2 ranged from 6.68-67.1 ml), possibly because of the third dimensional component of the tumor that can't be assessed clinically. Also, they found that with MTV, even if the tumor had a complete response to chemo radiation, patients tended to have a distant failure at a later date. They found that MTV did not have a correlation with SUV, and patients who had a high SUV but a low MTV had good clinical outcomes.

La et al. [55] studied the role of pre-treatment MTV in predicting recurrence and/or death in locally advanced HNSCC. They included 85 patients of all sub-sites, the majority of which were oropharynx and nasopharynx. They showed that an increase of MTV by 17.4 ml was associated with a 1.9 fold increase in likelihood of recurrence and 2.1 fold increase in likelihood of death. They also demonstrated a significant correlation between MTV and survival (both overall survival and disease-free survival). They found a significant correlation between MTV and GTV (gross tumor volume) but no relation between SUV and outcomes.

Murphy et al. [56] studied 47 patients of head and neck cancer (majority being oropharynx and nasopharynx) treated with radiotherapy or chemo radiation, who underwent pre- and post-treatment FDG PET CT scans. They found that $MTV_{2.0}$ (tumor volume having SUV threshold over 2.0) was a robust predictor of disease progression and death. An increase in $MTV_{2.0}$ of 21 ml was associated with increase risk of disease progression and death. In non-nasopharyngeal carcinoma patients, $MTV_{2.0}$ of over 18 ml was associated with significantly lower disease free survival and overall survival.

Park et al. [57] in their study on 81 patients of advanced laryngo-hypopharyngeal tumors determined MTV and relation to 3-year locoregional and overall survival. They found that MTV was an independent prognostic factor for both. 58% of these patients, however, were treated with surgery. Their cut-off for MTV for risk stratification was also 18 ml.

Tang et al [58] studied 83 patients of HNSCC before definitive radiotherapy. Their study had a similar MTV cut-off of 17 ml, above which risk of recurrence and death were 2.1 and 2 times more likely. They also found that prognostic significance was only based on the MTV of the primary tumor and not the nodal metastases. They also studied MTV and outcomes specifically in p16 positive tumors, however there was no significance. There was also no correlation between outcomes and p16 positivity.

Choi et al. [59] studied 56 patients with locally advanced HNSCC treated by surgery. Their cutoff for MTV was also 20.7 ml. This correlated with disease free survival and overall survival. Other comparisons were similar. Romesser et al. [60] compared SUV and MTV/GTV in 41 advanced HNSCC patients undergoing IMRT. They found that GTV of fewer than 22.2 ml had good 2 year loco regional control rates and overall survival compared to those above this value. The corresponding MTV was 7.2 ml.

Overall, MTV has been shown to be a significant predictor of outcome, in spite of variation in treatment modality, both in a pre- and post-treatment setting. It has a durable response and in a majority of studies correlates well with GTV but has no correlation with SUV. It has consistently been used to predict short and long term outcomes, but has yet to be used for early identification of those likely to fail on organ preservation therapy for treatment intensification or change in treatment modality - further studies are required.

Total lesion glycolysis

Total Lesion Glycolysis (TLG) is derived from the product of the SUV with metabolic tumor volume. This overcomes the limitation of some SUV measurements like SUV_{max}, a single pixel measurement, and is likely to be an aggregate estimation of activity in the entire tumor, incorporating both volumetric and metabolic activity into a single parameter, like MTV.

Abd et al. [6] measured the TLG in 126 oral cavity SCC patients who were undergoing surgery. They formulated a scoring system in multivariate analysis which included primary tumor TLG > 71.4 ml, nodal positivity and nodal SUV_{max}>7.5, and patients were assigned scores between 0-3. The patients with score of 3 had a 32 fold higher risk of cancer death than subjects with a score of 0. Also, in patients who had a score of 3, the mean TLG tended to be higher among those survived less than 9 months, compared to those who survived at least 9 months.

Lim et al. [62] reported SUV_{max}, MTV and TLG from 176 patients of oropharyngeal SCC treated with chemoradiation. They demonstrated that MTV and TLG were independent predictors of mortality. But unlike other studies they did not provide a cutoff value, and noted that when TLG doubled, the hazard ratio from distant metastases and mortality were 1.6 and 1.7 respectively.

Hanamoto et al. [63] analyzed 118 patients of HNSCC, included nasopharyngeal cancer, oropharyngeal and laryngohypopharyngeal cancer who underwent chemo radiation. They noted that high MTV (>25 ml) and high TLG (>144.8g) were independent, significant predictors of incomplete response compared to lower values.

Discussion

A major hurdle to acceptance of pre-treatment FDG PET as a prognostic tool in patients of HNSCC undergoing organ preservation protocols has been heterogeneity in the design of studies and their findings. As newer FDG PET parameters like MTV and TLG were developed, the results became more homogenous. Pak et al. [64] in their meta-analysis of thirteen studies and 1180 patients that MTV and TLG were independent indicators of progression and recurrence. High SUV was also shown to be associated with a higher risk of death, but could not robustly predict either recurrence or progression. This was also shown by the meta-analysis of prognostic impact of SUV on outcomes in 1415 patients by Xie et al. [65].

In the era of organ preservation protocols, the role of post-treatment FDG PET is established, while that of pre-treatment FDG PET is controversial; however early prediction of response to treatment and prognosis may be a valuable aid in predicting treatment failures. Incorporation of PET into radiation planning may also be more feasible than it was previously, given the better quality of CT imaging used for fusion and the availability of MRI for fusion.

No studies have compared directly compared the FDG PET parameters with need for surgical salvage, however reduced locoregional control rates may be considered a surrogate marker for this. Additionally, given recommendations that post-operative FDG PET for organ preservation protocols should be performed at 12 weeks after completion of therapy [66], identifying individuals with a poor prognosis may be important to prevent disease progression during this period.

From a prognostic standpoint, recent studies correlating FDG PET findings with molecular biomarkers have shown promise -Rasmussen et al. [67] showed in 100 cases of HNSCC that SUV_{max} had a negative correlation with Bcl-2 and p16 expression and a positive correlation with β-tubulin-1 levels and Han et al. [68] demonstrated in 32 patients of T2 tongue that SUV_{max} correlated well with HIF-1α, a hypoxia associated factor associated with radiation resistance. This work has led to increased understanding of tumor biology, however clinical applications are still under investigation.

Conclusion

Given the durability and safety profile of FDG PET, availability and cost are likely major inhibitory factors preventing more widespread use. With increased access to this technology and a fall in cost, its use in prognostication and predicting response to organ preservation protocols in HNSCC seems reasonable, as planning surgical salvage early may reduce extent and morbidity associated with surgery. Technical improvements have made the use of FDG PET in radiotherapy planning more reliable and feasible. Further study, especially correlation between FDG PET parameters and the need for surgical salvage, may be valuable in refining this as a tool for more routine clinical practice.

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