Primary Tumor Standardized Uptake Value Predicts Survival in Head and Neck Squamous Cell Carcinoma

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Introduction

Head and neck cancer is one of the most common cancers worldwide, accounting for over 550,000 new cases and 300,000 deaths per year [1]. In the western world, more than 90% of head and neck cancers are head and neck squamous cell carcinomas (HNSCCs). As with other types of cancer, the most important prognostic factor identified is the stage of the disease. However, this approach continues to be limited by outcome heterogeneity within stage categories, hampering accurate prognostication for individual patients [2]. Thus, we need additional prognostic factors that can predict treatment outcome. The development of functional imaging studies, particularly positron emission tomography (PET) with the glucose analogue 2-[18F]fluoro-2-deoxy-D-glucose (18F-FDG), has provided a useful tool for several malignancies. PET scanning offers the ability to noninvasively study the physiology of cancers [3]. The standardized uptake value of 18F-FDG (SUV), as measured by PET, has been shown to be linked to various cellular characteristics, such as cell viability [4] and proliferative activity [5]. The SUV is a semi-quantitative measure of the tissue deoxyglucose metabolic rate. It has been suggested that tumor FDG uptake may have prognostic significance, because patients with high FDG uptake generally have a less favorable outcome [6].

Other retrospective studies have explored the prognostic significance of the SUV, but most of these reports only include a small number of patients. Based on these considerations, we undertook a systematic review of the literature on the use of 18F-FDG-PET scans for predicting survival, and performed a meta-analysis of the acquired data to determine the prognostic value of the primary tumor SUV in patients with head and neck cancer.
Materials and Methods

Search Strategy

We searched PubMed, Embase, the Cochrane Controlled Trials Register and OVID without language restrictions. We employed both medical subject headings and free-language terms for ‘HNSCC’ (i.e., ‘head and neck cancer’, ‘head and neck carcinoma’, ‘squamous cell carcinoma’) in combination with each of the following: ‘positron emission tomography or PET or PET imaging tomography’ and ‘FDG-F18 or FDG or 18F-fluorodeoxyglucose or 18F-FDG’ and ‘SUV or standardized uptake value’ as search terms. The references reported in all the identified studies were used to complete this search, which ended in May 2014. Further searches were done by scanning the abstracts of major ENT (ear, nose, throat) and nuclear medicine meetings.

Inclusion and Exclusion Criteria

To be eligible for the systematic review, a study had to: (1) be limited to HNSCC with any stage or any histological grading; (2) assess the relationship between pretherapeutic SUV and survival at least in univariate analysis; (3) provide SUV referring to the primary tumors; and (4) demonstrate the use of all modalities of care.

Abstracts were excluded as they could not be expected to provide sufficient details for assessing methodology or the relative information for performing meta-analysis. Furthermore, we carefully checked the possibility of the duplication of a patient’s data through reports of the same cohorts in different publications. This led to the suppression of 1 article, although no reference to such duplication was reported by the authors.

Quality Assessment

To gain a good quality assessment, 7 physicians and 1 biostatistician reviewed each publication to assess methodological quality, and to extract the most important information determining the clinical and PET characteristics. A methodological quality scale was designed for this study using the variables most important information determining the clinical and PET reports. The clinical reports included: the distribution of the expected prognostic factors (age, gender, stage, performance status, histological grading, and weight loss); tumor stage description; staging characteristics (definition of the size of pathological metastasis, systematic use of the head and neck computed tomography (CT) for head and neck staging, systematic metastatic work-up, systematic use of a CT or magnetic resonance imaging (MRI) for distant metastasis, histological confirmation of metastasis, and if the analysis of the relationship between SUV and each expected prognostic factor was performed without knowledge of clinical results and vice versa (double blind)); and a description of results of survival analyses (number of patients, number of survival, follow-up duration, number of patients lost to follow-up, univariate and multivariate analyses, description of statistical tests, definition of survival, SUV cutoff definition). The PET reports included: patients characteristics (weight/height, glycemia, histological subtype). 18F-FDG-PET acquisition protocol characteristics (injected dose of 18F-FDG, delay between injection and data acquisition, fasting duration), and technical parameters (investigation area, delay between the head and neck CT and PET acquisition, SUV formula, type of PET engine, duration of emission time, duration of transmission time, attenuation and reconstruction parameters, type of SUV). The clinical and PET reports were scored on the basis of 21 and 14 points, respectively. A value between 0 and 2 was attributed to each item. The scores were expressed in percentage of the maximal theoretical value that can be obtained. When the results of a particular study were reported in more than 1 publication, only the most recent and complete data were included in the meta-analysis.

Statistical Analysis

Data were extracted by Zhang and Nie, and discrepancies were discussed and resolved by Li and Geng. Data were entered into the Cochrane Collaboration review manager program RevMan 4.2.2. We measured the impact of SUV by RR between the survival distributions for the 2 groups (low or high SUV). For each trial, this RR was estimated by a method chosen depending on the results provided in the publication. The most accurate method involved determining the total number of events and the number of patients at risk in each group, which allowed calculation of the RR. If the only exploitable data were in the form of graphical representations of survival distribution, we extracted the corresponding rates at certain specified times to reconstruct the RR estimate and its variance, with the assumption that the rate in patients observed was constant during the study follow-up. Accepting the null hypothesis of the homogeneity of the treatment effect across the various trials, the individual RR point estimates were combined using the RevMan 4.2.2 to obtain a global RR estimate for the treatment effect. The RR was calculated using a fixed-effect method. If a test showed significant heterogeneity (p < 0.05), a random-effect method was applied. The impact of SUV on survival was considered to be statistically significant if the 95% confidence interval (CI) for the overall RR did not overlap 1. All reported p values were two-tailed. Finally, funnel plot asymmetry was used to detect any publication bias in the meta-analysis.

Results

A total of 9 articles [8–16] related to SUV study in HNSCC were retrieved. 2 studies were excluded from the analysis due to patient duplication [15] and the required data being inaccessible [16]. 7 studies, published between 1997 and 2014 were potentially eligible for this review. The sites of primary tumors in these studies included the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, and maxilla. Survival time ranged from 1 to 94 months in

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<th>Study</th>
<th>Type of SUV</th>
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<td>Minn 1997 [8]</td>
<td>SUVmax</td>
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<td>median</td>
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<tr>
<td>Allal 2004* [9]</td>
<td>SUVmax</td>
<td>weight</td>
<td>median</td>
<td>4.76</td>
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SUV = standardized uptake value.
*Includes 3 patients with unknown primary tumors and 2 with T1–2 tumors, and in these 5 patients the SUV of the lymph nodes was used as reference.
*Includes 3 patients with unknown primary HNSCC of the neck, and the SUV was determined based upon the neck node disease.

Table 1. Main SUV characteristics reported in the 7 publications assessable for meta-analysis
these study. For the present investigation, SUVs referred to the primary tumor, except for those for 8 patients (6 with unknown primary tumors and 2 with T1–2 tumors) in whom only the lymph nodes demonstrated increased uptake. Consequently, for these 8 patients the SUV of the lymph node was used as reference for a correlation with survival. The main SUV characteristics reported in the publications are described in table 1.

The methodological quality of the studies was moderate. Overall, the median quality score was 63%, ranging from 53% to 71%. The respective median values for the clinical and PET reports were 69% (range 52–74%) and 68% (range 54–71%). The methodological quality conditions of the 7 eligible studies are described in table 2.

The combined RR of the survival from the 7 reports was 0.53 (95% CI: 0.46–0.62). The combined RR was calculated using a fixed-effect method. The combined RR confirmed that high FDG uptake on PET is a marker for poor outcome in primary HNSCC. The results are detailed in figure 1. The funnel plot exhibited a symmetrical distribution, indicating that there was no evidence of any substantial publication bias. The results are detailed in figure 2.

Discussion

Over the past decade, FDG-PET has become an important tool for staging tumors in patients with HNSCC. In vivo imaging of human tumors with FDG-PET is a clinical extension of classical studies on carbohydrate metabolism. It was demonstrated that the high rate of glycolysis characteristic of tumor growth could be exploited for malignancy grading using PET [17]. The specific goal of our study was to evaluate the potential of SUV as a prognostic marker. The current meta-analysis confirmed that increased SUV of the primary tumor is a factor for a poor prognosis in patients with HNSCC.

Under the balanced circumstances of glucose metabolism, 18F-FDG is phosphorylated, preventing glucose release and further metabolism. Metabolism retention products of FDG are consistent with the amount of glucose consumed by the cells. Therefore, 18F-FDG can reflect the status of glucose utilization in vivo. SUV is a semi-quantitative index that shows the characteristics of the 18F-FDG tracer uptake, hence approximating the actual glucose metabolic rate in tissues. Factors affecting the SUV include the region of interest outlined, focus size, system resolution, reconstruction algorithm, patient factors (body weight, lean body weight, body surface area), non-tumor uptake caused by activation, and acquisition time after drug injection. The time between injection and PET data acquisition in the eligible articles ranged from 45 to 60 min. That makes SUV closer to the glucose metabolic rate. However, SUV estimates suffer from poor reproducibility between centers because of the lack of standardization of the acquisition and processing protocols used for its assessment. This poor reproducibility was shown by the broad range of threshold values that have been used in the literature to distinguish between patients with low and high survivals.
To be a functional prognostic factor for routine practice, either a single SUV threshold that allows distinction between patients should be adopted, or optimized methods for determining the threshold need to be established for each center. To set a common threshold, most variable factors impacting the SUV estimations should be resolved or at least controlled. In this sense, narrowing the large variability currently affecting SUV estimates would probably enhance the prognostic value of SUV. In our study, we could not take into account the variable conditions in which the SUV were obtained, due to the poor quality scores of the PET reports. Despite of the above-mentioned variability, we were able to show that SUV was correlated with patient survival. Based on the SUV thresholds used in each corresponding study, our research regimens calculated an RR for each study center to control the deviation of data, which to some degree suppressed the difference in threshold factor used in different centers. By doing so, we could ignore the difference of SUV’s between different centers and demonstrate that SUV is certainly worth considering as a prognostic factor.

Literature-based meta-analysis has the advantage of including published trials available for analysis, the results of which can be checked by everyone. In our meta-analysis, it is possible that some bias may have occurred. Generally, for meta-analyses, a funnel plot can be used to indicate publication bias. In the present investigation, publication bias cannot definitely be ruled out because of the small number of included studies and the low power of the tests to detect it. Some studies were not included because separate data for head and neck cancer patients could not be obtained. Another limitation of our study is the lack of data from multicenter and large-scale perspective studies.

In conclusion, this meta-analysis provides evidence for a potential value of FDG uptake, as measured by the SUV, in predicting survivals in head and neck carcinomas. We are currently planning a meta-analysis based on the individual patient data that will potentially reduce biases related to literature-based meta-analyses.

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Disclosure Statement

The authors declare that they have no conflict of interest.

References