

PRIMARY TUMOUR AND BONE MARROW FDG UPTAKE IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: IS THERE A RATIONALE FOR A CORRELATION?

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BACKGROUND AND AIM

Tumour diagnosis has been enormously improved by the availability of new imaging modalities such as the Positron-Emission-Tomography (PET); PET cameras are often combined with a Computerized-Tomography (CT) scanner, thus providing a simultaneous PET and CT fusion image that further improves the diagnostic potentiality of these tools. PET scan is obtained by administering radiopharmaceuticals labelled with positron-emitting isotopes (such as ¹⁸F). The most popular radiopharmaceutical for tumour diagnosis is ¹⁸F-deoxy-glucose (FDG). FDG is avidly taken up by tumour cells because of increased glucose metabolism; nevertheless several false positive uptakes can be observed in the daily practice, mainly due to inflammatory cells, also exhibiting high glucose metabolism. In order to help discriminating between inflammation and cancer a quantitative measurement of FDG uptake has been standardized (Standardized-Uptake-Value, SUV). SUV is usually higher in cancers than inflammation. There are however several methods described for calculating SUV and little is known about the prognostic significance of elevated SUV. The aim of this study was to propose a statistical measurement of the SUV over Head-and-Neck tumors and to evaluate its correlation with bone marrow SUV and peripheral white-blood-cell count.

METHODS

Thirty-five patients suffering from primary, untreated squamous cell carcinoma of the head and neck (SCCHN) underwent a PET examination as part of the routine staging procedure. Tumour SUV max and mean values as well as SUV mean values calculated over the vertebral body of L3, were obtained in all patients and correlated to serological, clinical and pathological findings as well as to each other. Pet data were processed using MIMVISTA software. The maximum tumour SUV was obtained by drawing a region of interest (ROI) over the most intense slice of the primary lesion, using CT as a reference. The mean tumour SUV value was defined using a “region growing” tool; the ROI was drawn automatically, considering all the voxels contained between the maximum SUV and a threshold of 75% of the maximum value itself. A mean SUV value was also obtained with the same procedure for vertebral body L3 by drawing a ROI over the transaxial slice containing the central part of L3 as evidenced by CT.

RESULTS

We studied 26 men and 9 women (mean age 62 years). Six patients presented with stage 1 disease, five presented with stage II disease, four patients with stage 3 disease and 20 patients suffered from stage IV disease at the time of diagnosis. SUV max values of the primary tumour ranged from 3.2 to 33.0 (mean 10.4). SUV mean values of the primary tumour ranged from 2.6 to 24.6 (mean 7.8). Both SUV mean and SUV max values of the primary tumour did correlate with tumour stage ($p=0.05$), while there was no significant difference for different histological grades ($p=0.78$ and 0.315 , respectively). SUV max of the primary tumour did not correlate with any of the blood parameters listed, such as Hb, WBCs, Platelets, RBCs, nor with the tumour diameter. In contrast,

SUV mean (average activity: 1.40, range: 0.7 to 3.51) of the primary tumour correlated significantly with WBC count ($r=0.44$; $p=0.011$). Mean SUV bone marrow activity correlated significantly with both SUV mean and max values of the primary tumours (respectively $r=0.473$ ($p=0.04$) and $r=0.591$ ($P=0.000$)). The correlation coefficients obtained were not significantly different from each other ($z=-0.66$, $p=0.51$). SUV mean bone marrow activity did not differ significantly between patients presenting with different stages of disease nor with different histological grade.

SUV mean bone marrow activity was not related to white blood cell-, red blood cell- or platelet counts, nor to Hb level or tumour diameter.

DISCUSSION

In 65% of patients with tumours of the head and neck, granulocyte monocyte colony stimulating factor (GM-CSF) is known to recruit CD34+ natural suppressor cells that suppress CD4+ cell activity (1, 2). It is worth noting that a large proportion of SCCHN tumors produce high amounts of GM-CSF, but the corresponding blood levels of GM-CSF are not significantly increased when compared to normal controls (3), while the level of CD34+ cells in primary SCCHN has been found to be predictive for recurrence or metastasis (6). Circulating CD34+ cells are then recruited from the blood into SCCHN by vascular endothelial growth factor (VEGF), whose production is increased as well as glucose metabolism by the tumour itself (1, 4).

We observed a weak but significant relationship between WBC count and SUV mean of the primary tumour; it may be related to tumour production of GM-CSF and VEGF driven recruitment of CD34+ cells into the tumour. SUV mean values of bone marrow significantly correlated to the mean and maximum SUV values of untreated primary SCCHN tumours but not to WBC-, RBC- or platelet count nor to the blood level of Hb. None of the blood parameters, and thus indirectly none of the stimulating factors, was significantly increased, probably explaining the lack of relationship between SUV mean values of bone marrow and the level of blood cells. The relationship between SUV mean and max of the primary tumour and SUV mean values of bone marrow may be related to VEGF production. High VEGF levels increase, directly or through GM-CSF, the absolute number of bone marrow progenitor cells, and thus also likely bone marrow FDG uptake, respectively by stimulating the division and by prolonging the survival of bone marrow cells. Recently VEGF has also been implicated in the tumour metastasis process through direct interaction with the bone marrow; VEGF in collaboration with TGF β and TNF α , stimulate normal fibroblasts to produce fibronectin, subsequently allowing cell to cell attachment by integrins expressed by specific subsets of bone-marrow derived cells (7,8). Bone marrow cells then create the proposed 'pre-metastatic niche' joined by tumour cells to form a metastasis. These data further support the link between hyper-glycolysis, VEGF production and metastasis formation, providing a rationale for the higher level of FDG uptake in more advanced stages as evidenced by present series as well as by other authors (5).

CONCLUSIONS

In untreated SCCHN patients, FDG SUV mean values of the primary tumour correlate significantly with WBC count. SUV mean values of bone marrow are significantly correlated to the mean and maximum SUV values of untreated primary SCCHN tumors but not to WBC-, RBC-, platelet-count or to the blood level of Hb and CT-findings. Although the complexity of the underlining biological mechanisms does not allow a definitive explanation, the analysis of the recent literature about this topic gives a plausible rationale for the correlation observed.

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