Functional imaging to predict treatment response after (chemo) radiotherapy of head and neck squamous cell carcinoma

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Head and neck squamous cell carcinoma (HNSCC) refers to malignant tumors that arise in the upper aerodigestive tract including oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses. About one third of the patients present with early stage disease (stage I and II), while two-third presents with advanced disease (stage III and IV). In the past the majority of patients with advanced stage disease were treated with a combination of surgery and radiotherapy, often with the costs of functional and cosmetic morbidity, inducing a diminished quality of life. Irresectable (technically inoperable) HNSCC was treated by radiotherapy with or without chemotherapy. Nowadays, in an attempt to decrease the morbidity non-surgical treatments are increasingly applied, also to resectable HNSCC, with considerable complete remission rates. It appeared that intensified radiotherapy schemes and combinations of chemotherapy and radiotherapy all contribute to an increased remission rate. In advanced HNSCC locoregional control rates about 50% are reported. However, also non-surgical treatment is not without acute and long-term side effects, leading to compromised quality of life.

In patients with functionally irresectable HNSCC (resectable but high morbidity of surgical treatment expected), a non-surgical treatment with salvage surgery for eventual residual or recurrent disease in reserve is preferred. However, in case of residual or recurrent disease salvage surgery is only possible as curative treatment in about half of the patients. Moreover, the complication rate of salvage surgery after chemoradiation is high, with wound healing problems as a well-known complication in irradiated patients. Another important disadvantage of salvage surgery after radiotherapy is the fact that, postoperative radiotherapy although indicated by adverse histopathological findings is rarely possible, thus limiting the outcome of this treatment.

A better selection and individualized treatment may spare a certain number of patients from futile extensive radiotherapy with or without chemotherapy and its morbidity, decreasing the complication rate of surgical treatment and reserving radiotherapy for the postoperative setting if indicated. A reliable predictor for outcome after chemoradiation is needed to select patients with resectable tumors who are likely to benefit from primary nonsurgical treatment (1). Valuable predictive factors provide information on the outcome of therapy in an individual patient allowing avoidance of over- as well as under-treatment.

Conventional predictive factors for locoregional control include T-stage, N-stage and tumor volume, as measured by CT or MRI. Due to the limited predictive value of these factors room for improvement remains. The predictive value of molecular biological markers is currently under investigation. Functional imaging modalities which are reported to have predictive value both pretreatment and early and late during treatment, include positron emission tomography (PET), diffusion weighted (DW) MRI and dynamic contrast-enhanced (DEC) MRI. These functional imaging techniques provide, complementary to morphology as evaluated by CT and MRI, information on the underlying biology such as metabolic activity, cellularity, vascularity and oxygenation, all potential mediators of chemoradioresistance. Evidence is emerging for functional imaging in HNSCC in providing accurate staging, prediction of treatment response and identification of residual and recurrent disease. However, a better understanding how to use functional imaging in the individualization of treatment for HNSCC is still required (2).

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Tumor metabolism is a potential predictive factor and can be studied with PET. In malignant tissue, up-regulation of glucose uptake through overexpression of glucose transporters (Glut) is an early event. 18Fluoro-2-deoxyglucose (FDG) is the most widely used PET tracer in oncologic PET studies and can be used to measure the glucose metabolism in malignant tissues. Quantification of tracer uptake can be done in several ways, from pure visual analysis to simple calculations of uptake level using a Standardized Uptake Value (SUV; i.e., the ratio of measured uptake in a static scan obtained 60 min after FDG injection over the injected dose and normalized for volume of distribution, e.g., body weight) or more complicated kinetic analyses providing the metabolic rate of glucose uptake (in $\mu mol \cdot min^{-1} \cdot g^{-1}$). In untreated HNSCC, a high correlation (r=0.8) was found between complicated kinetic modelling (Patlak analysis) and simple calculations with SUV in primary tumors (3).

There is ample proof of principle that quantitative PET measures have clinical value beyond visual interpretation. This pertains to prognostic (typically inverse relation between FDG uptake level and outcome) as well as predictive aspects (response monitoring). In HNSCC, high SUV predicts for significantly worse outcome and might be used for individualized treatment planning (4-7). FDG uptake, as measured by SUV, prior to radiotherapy with or without chemotherapy for stage II-IV HNSCC has a potential value in predicting local control: local control rates of 86% and 55% for low (≤ median) and high SUV are reported, respectively (8). Recently, Picchio *et al.* (9) found in a series of 19 head and neck cancer patients undergoing FDG-PET-guided radiotherapy that SUV of the primary tumor predicted outcome well.

PET quantification with SUVs is affected by many technical and physiological factors. As a result some of the variations in the literature on SUV-based patient outcomes are explained by differences in FDG-PET study methods (10). These differences concern patient factors (e.g., plasma glucose levels), time interval between injection and scanning, image reconstruction technique, image quality and SUV measure used. Therefore, different studies are difficult to compare and meta-analysis will not be possible. In designing prospective multicenter studies to examine the value of SUV in the prediction of treatment outcome, calibration of PET-scanners and standardisation of PET-scanning protocols should be performed. Because it has now been recognized that SUV results highly depend on several aspects that need to be controlled, standardized

FDG-PET scanning and quantification protocols are developed to determine the optimal cut-off level and clinical value of SUV in treatment planning of HNSCC patients (11). Using these guidelines, larger multicentre studies and meta-analyses are possible to define clinically appropriate, externally validated thresholds and criteria.

Another imaging modality which is reported to have predictive value both pretreatment and early and late during treatment, is DW MRI. DW MRI provides maps of microscopic water motion within tissues. Higher cellularity (e.g., malignant tissue) is generally associated with more restricted diffusion [lower apparent diffusion coefficient (ADC) values]. DW-imaging is an attractive technique because it can be performed within a few minutes and can be easily incorporated into routine head and neck MR imaging protocols. However, the head and neck region is particularly difficult for performing EPI (echo planar imaging)-DW imaging acquisitions because it is very inhomogeneous, containing a variety of tissues that include bone, fat, muscle, glandular tissue and air. This can yield images with strong susceptibility artefacts from the many air-tissue boundaries, as well as from dental fillings and surgical implants. Moreover, the head and neck area is subject to a number of movement-related problems: jaw movements, swallowing, breathing, coughing and speaking. Resulting distortion and failed fat-suppression artefacts can cause nondiagnostic imaging. If susceptibility artefacts are too detrimental, a non-EPI sequence, so-called turbo spin-echo DW sequences (e.g., half Fourier acquired single-shot turbo spin-echo), can be used (12).

Differences in tissue water mobility, as characterised by DW MRI, can be quantified using an ADC. Hypercellular tissue is characterized by a low ADC, while high ADC is found in hypocellular tissue associated with an increased resistance to treatment.

Kim *et al.* (13) showed in a recent study with 33 HNSCC patients treated by chemoradiation and a median follow-up of 12 months a significantly lower pre-treatment ADC in lymph node metastases of complete responders as compared to than partial responders. A significant association was also found between pre-treatment ADC and local treatment failure in another study with 38 patients (14). However, these findings could not be confirmed in a larger study with 50 HNSCC patients by King *et al.* (15). In a recent study, Chawla *et al.* (16) did not find a significant difference in ADC values between responders and nonresponders to chemoradiation in 32 HNSCC patients. The authors suggest that this insignificant difference may be due to

high intratumor heterogeneity or different clinical follow-up times (defining treatment responsiveness). Another potential factor hampering data analysis is the use of different scanners. ADC values may be affected by the selected technique and scanner, due to differences such as gradient systems, coils, pulse sequence designs, imaging parameters and artifacts related to susceptibility effects.

DCE MRI provides a perfusion parameter K^{trans} that reflects a combination of tumor blood flow and microvascular permeability which are different in malignant tissues as compared to normal tissues. Other perfusion parameters which are different in malignant tissue are extracellular extravascular volume fraction (v_e) and plasma volume fraction (v_p). Several studies reported that HNSCC patients with elevated pretreatment tumor blood flow, increased blood volume and higher K^{trans} values showed improved response to chemoradiation (17,18). Chawla *et al.* (16) studied the predictive value of different DCE MRI parameters (K^{trans}, v_e and v_p) to respond to chemoradiation in 32 HNSCC patients. Unfortunately, only median pretreatment volume transfer constant (K^{trans}) was significant higher only in lymph node metastases of responders relative to those of nonresponders. Other perfusion parameters were different but not significantly. Although efforts were made to correct for motion artefacts, in 17% of the patients no reliable DCE MRI data could be achieved because of motion from swallowing and coughing. More stringent acquisition and postprocessing tools are needed to reduce the dropout rate in future studies.

Chawla *et al.* (16) showed that in HNSCC patients treated by chemoradiation, although DW and DCE MRI parameters were not able to differentiate responders from nonresponders, a substantial higher discriminative accuracy (correct classification of 75%) was observed when incorporating these tumor and lymph node parameters in a multivariate regression analyses. It has also been suggested that a combination of DCE MRI and PET may provide additional information of the tumor microenvironment. A multiparametric data analysis approach may use the unique strengths of different imaging techniques and obtain greater discrimination accuracy in differentiating responders from nonresponders. Recently PET-MRI had been introduced which combines the unique metabolic imaging capabilities of PET with excellent soft tissue contrast and functional information of MRI. Platzek *et al.* (19) reported on a feasibility study which demonstrated that PET-MRI of the head and neck is feasible without impairment of PET and MRI quality. It may be expected that the highest value of such combined imaging for patients with head and neck cancer may be found in prediction of response after chemoradiation, in early and late evaluation after treatment with chemoradiation and when there is suspicion of tumor recurrence (20).

Functional imaging has potential in predicting response to chemoradiation in HNSCC patient.

However, technical improvements for DCE MRI, ADC correction for different MRI scanners and standardization of these techniques, as proposed for FDG-PET and SUV measurements, are needed to perform useful meta-analysis and multicenter studies.

Acknowledgements

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