Nodal staging in head and neck squamous cell carcinoma by combining different imaging techniques

Impact paragraph

Research (aim and conclusion)

Squamous cell carcinoma (SCC) of the head and neck (HN) are derived from mucosal epithelium in the oral cavity, pharynx and larynx. Tobacco consumption, alcohol abuse or both will increase the risk for oral cavity and larynx cancer. HNSSC of the pharynx can be associated with human papillomavirus infection (HPV) and HNSCC can be separated into HPV-related and non HPV-related tumors.

Before treatment, the origin of the tumor and histopathology of the tumor as well as tumor size and tumor spreading have to be defined. Tumor stage (TNM) is reported as tumor size(T), nodal metastases (N) and distant metastases (M).

The presence of cervical lymph node metastases next to tumor volume, is one of the most important predictors for survival.

For nodal staging computer tomography (CT), ^{18}Fluordeoxyglucose positron emission tomography (PET), Magnetic resonance imaging (MRI) ultrasound (US) and ultrasound guided fine needle aspiration cytology (FNAC) are commonly used.

PET-CT has a very good performance to detect lymph node metastases but in small nodes it is still difficult to distinguish between reactive (benign) nodes and small metastases, therefore node selection for FNAC is still very challenging and nodes with small metastases can be missed and remain as occult metastases.

Real time image fusion with CT, PET-CT or MRI on one hand and ultrasound on the other hand, is a relatively new imaging technique. Although image fusion to guide biopsies and therapeutic interventional procedures is widely used, real time image fusion of PET-CT and ultrasound in head and neck imaging is rarely used and no literature on this topic has been published before.

With Power Doppler ultrasound vascularization of tissue can be shown. In malignant tissue de vascularization pattern will change. Micro flow imaging with ultrasound is a new method to depict micro flow in small vessels.

In our thesis we wanted to investigate if these new imaging methods will help to improve the detection rate of lymph node metastases and improve sensitivity.

In **chapter 2** we were able to show that real time image fusion of PET-CT with ultrasound is feasible. This implicates that fused-USgFNAC of PET-positive nodes can be performed with more confidence and the detection rate of lymph node metastases will be improved.

In **chapter 3** we defined SUVmax cut-off values for nodes which have to be punctured to minimize unnecessary punctures in PET-positive reactive nodes. We found that all nodes with a SUVmax below 2.87 were benign and all nodes with SUVmax above 10.6 were malignant at USgFNAC. Consequently punctures could be avoided in those nodes but still we have to deal with the group of nodes between 2.87 and 10.6, in this group malignant as well as reactive (benign) nodes were present.

In **chapter 4** we investigated if DW-MRI would help to distinguish between malignant PET-positive lymph nodes and reactive PET-positive lymph nodes. DW is a method to measure the diffusion of water molecules in tissue. Tumor tissue has generally a higher cellularity than normal tissue and diffusion is therefore restricted. The apparent diffusion coefficient (ADC) reflects the quantitatively analyses of this restricted perfusion, and tissue with a higher cellular density has a lower ADC. We found significantly lower ADC values in PET-positive lymph nodes than in PET-negative nodes but only in the subgroup of non HPV-related nodes we were able to distinguish between malignant PET-positive and reactive/benign PET-positive nodes. This might be helpful for node selection of PET-positive nodes to be punctured.

In **chapter 5** we investigated the positive predictive value (PPV) of peripheral vascularization of lymph nodes using MFI and compared it with the PPV of nodal size and the absence of a fatty hilum of a lymph node. We were able to show that peripheral vascularization and hilum sign have a high predictive value to predict metastases and in cN0 PPV of peripheral vascularization is remarkable higher than in other ultrasound features . Because it is not time consuming and can easily be added to routine ultrasound work-up, it can be used routinely.

Relevance

The treatment of HNSSC is complex, it includes tumor surgery and surgery of the neck nodes (neck dissection (ND)), radiotherapy, chemo radiotherapy and immunotherapy.

Treatment planning is a balancing act between sufficiently radical treatment and preservation of functional structures. To preserve quality of life and to reduce treatment morbidity, treatment should be individualized. Next to tumor evaluation exact N-staging is essential to individualize treatment, which is improved with new imaging techniques.

If the probability of occult metastases is low enough, often 20% is mentioned, a watchful-waiting policy instead of elective neck treatment can be considered. With image fusion of PET-CT and ultrasound the detection rate of malignant nodes can be improved. Unnecessary Neck Dissection can be reduced which will lead to a higher life quality.

For sufficient radiotherapy planning and to reduce side effects of RT, nodal involvement per neck level has to be determined. Exact staging will help to limit RT fields to the neck levels of nodal involvement.

A higher detection rate of occult micro-metastases can lead to a lower recurrence of metastases with all the consequences for the patient and the public health costs.

Target population

The results of this thesis are relevant to several groups.

First the radiologist will be able to stage HNSSC tumors more exactly and with more confidence. Second, the treating health care professionals can plan treatment with more confidence. And thirdly the patient will be provided a more personalized treatment with less side effects and a higher quality of life. A higher detection rate of occult metastases will lead to a lower rate of tumor recurrence and will improve survival.

Scientific results are shared with the scientific community and provide new knowledge and inspiration for further investigations. Users of real time image fusion techniques and other new image techniques can share their experience and problems can be solved together with the industry.

Activities

The results of this thesis have been presented on the European congress of radiology (ECR) and published in peer-reviewed international journals. Results of this thesis can be implemented into the clinical practice and follow up projects can be performed in our Institute.

This thesis shows that the investigated new imaging techniques will help to improve nodal staging in HNSSC. But still there are many questions to be answered. Image fusion techniques for HNSSC nodal staging should be used more widely and to improve nodal staging of HNSSC research results should be shared nationally and internationally.