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PET/CT significance for planning radiotherapy of head and neck cancer

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The combination of positron emission tomography and computed tomography (PET/CT) offers metabolic mapping in addition to anatomic information of the primary lesion, nodal and distant metastases in patients with head and neck tumors, and may be therefore beneficial for radiotherapy planning. The aim of our study was to evaluate benefits of combined PET and CT imaging for staging and target volume delineation in this group of patients.

Fifty three patients (40 men and 13 women) with confirmed advanced, inoperable or non-radically operated head and neck cancer were assessed based on the results of PET/CT as well as standard diagnostic examinations. All patients were subsequently treated with intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) of 6 MV X-rays.

There was an agreement between the standard examinations results and results of PET/CT in 30 cases. In 23 cases there was disagreement either in tumor size, nodal involvement or presence of distant metastases. Results of the tumor size assessment differed significantly in 5 cases. There was no agreement found in nodal involvement in 10 cases. The cancer confirmed by standard examination was not found by PET/CT in 2 cases; 3 PET/CT positive findings were not confirmed by standard examinations. In 3 patients PET-CT revealed new distant metastatic disease. Based on PET/CT assessment we changed treatment strategy and applied potentially curative dose of radiotherapy to previously undiscovered regions in 9 patients. We decided to change the treatment intent in 3 cases and only palliative treatment was applied. Based on our experience and the literature review, PET/CT may be considerable contribution to the standard diagnostic procedures in approximately one third of cases.

Key words: PET-CT, radiotherapy treatment planning, head and neck cancer, IMRT

Radiotherapy is next to surgery one of the most effective modalities for treating head and neck tumors. This is due to the routine application of modern techniques, such as IMRT. Selection of different treatment modalities (surgery, radiotherapy, systemic chemotherapy and/or biological therapy) depends on the tumor localization, size, histological type of tumor, presence of nodal involvement and distant metastases, patient´s performance status, co-morbidities and of course on patient´s preference of the treatment modality [1,2].

Introduction of intensity-modulated radiation therapy made possible to deliver a high dose of radiation to the target volume, while relatively saving surrounding tissues. A potential negative impact of radiation therapy on surrounding critical structures unaffected by cancer is particularly important in the head and neck region. IMRT may deliver increased dose of radiation in the target volume and thus improve loco-regional control of the disease, while reducing common side effects, particularly xerostomia [3,4]. However, compared with conventional radiation techniques, it requires increased precision of the target volume delineation in order to reduce the risk of the relapse due to potential miss of tumor involvement. The basic imaging technique for the radiotherapy contouring and planning is computed tomography (CT), which is the only method that allows the calculation of the dose distribution taking into account tissue inhomogeneity. Unfortunately, CT is often not sufficient for precise tumor definition. Enlarged

inflammatory and/or reactive lymph nodes are often mistaken for malignity with lymph node involvement and small primary tumors may be missed or assessed insufficiently.

In addition to standard examinations, 18FDG (2-[18F]fluoro-2-deoxy-D-glucose) positron emission tomography (PET) can be used for disease staging. PET offers new diagnostic possibilities as it supplements the morphological imaging with a functional view. Numerous studies have shown that PET is superior to CT in identifying primary lesions and metastases in patients with head-and-neck cancer [5,6]. A hybrid PET-CT can provide additional information by combining PET and CT images and create results with increased geometric accuracy. High sensitivity and specificity of PET in oncology have been reported: sensitivity between 84% and 87% (18 402 patients examined) and specificity between 88% and 93% (14 264 patients examined) [7]. Some authors report even higher sensitivity and specificity of PET examination for assessing head and neck tumors and/or nodal involvement in respective areas [8,9].

PET is more accurate then computed tomography or magnetic resonance imaging and can be useful for identifying the primary tumor in patients presenting with metastases to cervical nodes. In addition, PET can identify unsuspected distant metastases and define regional disease in nodal regions. PET can detect additional tumors, especially in the lung and aerodigestive tract. The overall incidence of coincidental primary tumors is near 8%. PET is valuable for detecting recurrent disease because CT and MRI are limited in the postoperative neck. [10].

Data from the literature suggests that treatment planning based on PET-CT may considerably differ from the planning based solely on CT imaging [11,12].

Estimated 30% to 40% of radiation plans were modified due to the use of PET examinations in the planning process. In addition, the radiation dose increased by 10% to 20% can be specifically applied into PET-positive regions [13].

Main aim of our study was to evaluate benefits of combined PET and CT imaging for assessment of primary tumor volume and disease staging based on TNM classification in patients with head and neck tumors.

Patients and methods

From July 2006 to March 2008, a total of 53 patients (40 men and 13 women) with advanced inoperable or non-radically operated head and neck cancers were treated at our department. The median age was 56 years (ranging from 20 to 75 years). The basic clinical characteristics are summarized in tables 1 and 2. The histopathology examination confirmed squamous cell carcinoma (n=42), undiferentiated carcinoma (n=2), adenoid cystic carcinoma (n=2), lymphoepithelioma (n=5), and mucoepidermoid carcinoma (n=2). In 5 cases primary tumors were localized in nasal and paranasal cavity, 15 tumors were in nasopharynx or larynx, 12 primary tumors were localized in oral cavity, 3 were found in salivary glands, 15 were in oropharynx or hypopharynx and in 3 cases we found metastases in neck lymph nodes with unknown location of primary tumor (table 1).

PET-CT. A quality assurance and patient management protocol of our institution was applied in all cases together with standard PET-CT procedures. All patients provided a written consent to treatment and data collection. All processes were in compliance with ethical as well as legal requirement for non-interventional anonymous data collection in the Czech Republic. Standard pre-treatment staging included a contrast-enhanced CT scan of the head and neck, direct otorhinolaringologic endoscopic examination, ultrasound of the neck and chest X-ray. Following standard examinations, all fifty-three patients were examined in the treatment position on a hybrid PET-CT scanner Siemens Biograph duo LSO PET/CT at the PET Centre, Hospital Na Homolce Praha. Patients were immobilized with thermoplastic head and neck masks. Images were transferred to the Varian Eclipse planning system with the Helios module for inverse planning. The interpretation of PET-CT examination by a qualified radiologist was a basis for identification of involved regions. All scans were assessed by one radiologist. Target volumes and critical organs were contoured and IMRT plans were generated based on the fused images. Results were compared with the plans based on the standard diagnostic examinations.

Abnormal areas of primary tumor and nodal regions showing 18FDG uptake were contoured on PET/CT, assessing the gross tumor volume (GTV). CTVs (clinical target volumes) and PTVs (planning target volumes) were estimated based on the guidelines according to the involvement localization and disease stage [14]. If there was a disagreement between standard examinations and PET/CT, the stage was re-assessed by both radiographer as well as treating physician.

Table 1. Primary tumor

Involved site	Number of patients
Nasal and paranasal cavity	5
Nasopharynx	8
Larynx	7
Oral cavity	12
Salivary glands	3
Hypopharynx	5
Oropharynx	10
Metastases in neck nodes – unknown primary	3
Total	53
Histopathology	**Number of patients**
Squamous cell carcinoma	42
Undiferentiated carcinoma	2
Adenoid cystic carcinoma	2
Lymphoepithelioma	5
Mucoepidermoid carcinoma	2
Total	53

Table 2. Tumor stage based on CT

T-stage	
T1	2
T1b	1
T2	8
T2a	1
T2b	1
rT3	1
T3	10
T4	11
T4a	10
T4b	3
O(X)	5
N-stage	
N0	14
N1	5
N2	10
N2b	8
N2c	12
N3	4

Subsequent treatment. Following re-assessment, simultaneous integrated boost techniques were performed using either 2.2 Gy or 2.11 Gy per fraction to a total dose of 66-70 Gy. Intermediate and low doses of 54-60 Gy were individually defined to regions considered at high risk for microscopic disease.

The radiation dose was prescribed according to the International Commission on Radiation Units and Measurements (ICRU Report) [15,16].

Table 3. Changes in tumor stage based on PET-CT examination

TNM/tumor structure	Target volume change	Number of cases	Total number of cases
No change	No change	30	30 (56,6%)
N higher	N0→N1	2	5 (9,4%)
	N1→N2	1	
	N2a→N2b	1	
	N2b→N2c	1	
N lower	N1→N0	3	5 (9,4%)
	N2c→N1	1	
	N2→N0	1	
T higher	TX→T1	1	4 (7,5%)
	TX→T2	1	
	TX→T4c	1	
	T3→T4	1	
T lower	T4a→T3	1	1(1,9%)
M higher	M0→M1	3	3 (5,7%)
False positive	T	2	3 (5,7%)
	M	1	
False negative	T	2	2(3,8%)
Sum			53 (100%)

Results

Agreement between conventional staging (a contrast-enhanced CT scan of the head and neck, direct otorhinolaringologic endoscopic examination, ultrasound of the neck and chest X-ray) and the staging based on PET/CT examination was found in 30 patients (56.6%). Disagreement in remaining 23 cases was either in confirmation of the primary tumor site, its size, nodal involvement and/or presence of distant metastases (table3).

Based on PET/CT examination the tumor was significantly larger in 1 case and smaller in one another. Three new primary tumors not identified by conventional imaging techniques were confirmed by PET/CT.

The PET/CT examination revealed an extensive tumor destructing a scull base in one case, relatively small primary tumor at the base of the tongue and primary tumor in nasopharynx in the second and third case, respectively. These findings were subsequently verified by histology.

In 5 cases PET/CT confirmed higher nodal involvement; in 5 cases fewer nodal areas were affected. As a result of conventional staging enhancement by PET/CT, new distant metastases were confirmed in 3 cases.

PET/CT did not confirm one case of residual disease after surgery, and one case of the primary tumor identified by standard diagnostic methods. We regard them as falsely negative cases.

We were also unable to confirm two PET/CT positive findings in terms of a newly diagnosed primary tumor and one case of lung metastases either with CT or other conventional methods. We regard these findings as falsely positive.

The re-assessment of the tumor staging and the size of the primary tumor led to subsequent adjustment of the gross target volume in 15 cases (28.3%). Based on PET/CT assessment we changed treatment techniques. High dose volume was enlarged based on PET/CT assessment and potentially curative dose of radiotherapy was applied to involved region in 9 patients. In 3 cases the palliative treatment was recommended instead of curative approach.

Discussion

In our group of 53 patients, agreement between conventional diagnostic method findings and the PET/CT examination was found in 30 cases (56.6%). The primary tumor size was different in 9 cases. However, we regarded the results in 2 cases as false positivity and in 2 cases as false negativity. The nodal involvement was more extensive in 5 cases, less extensive in other 5 cases. New metastases were found by PET/CT in 3 cases. One case of distant lung metastasis identified by PET/CT was not confirmed by conventional methods including histology.

In 2010 Misono et al. observed 65 patients with head and neck tumors and compared PET findings with conventional diagnostic methods. Agreement was found in 63% of cases. Disease was found to be more extensive in 20% patients, 2% of

cases were regarded as falsely positive. Staging was decreased based on the PET examination in 6% [17].

Koshy et al. compared TNM classification of 36 patients, based on the conventional methods and PET/CT. They reported staging change in 36% of patients. However, this led to the target volume change only in 14% of patients [11].

Ha et al. tried to evaluate possible role of PET and PET/CT examination on treatment planning in patients with both small and advanced head and neck tumors. In their study of a group of 36 patients, the treatment plan was changed in 11 patients (31%); 6 patients were confirmed to have more extensive disease than initially expected based on the conventional methods finding. PET/CT assessed correctly extent of the primary tumor in all 18 patients who received surgical treatment. However, the extent of nodal involvement was shown correctly by PET/CT only in nine of them. Two patients did not have the lymphatic nodes removed for histopathology examination [6].

Deantonio and her colleagues observed 22 patients with head and neck tumors indicated for primary curative radiotherapy. They compared results of conventional diagnostic methods and PET/CT and reported a change in TNM classification in 5 cases. Overall gross tumor volume was higher by 6 cm^3 based on PET/CT, in comparison with CT based GTV [12].

It seems unlikely that a PET/CT assessment will always lead to increase of gross tumor volume. Some studies suggest that FDG-PET may lead to a decrease of the target volume and thus spare critical surrounding tissues. Several authors reported a significant reduction of targeted volumes in some of their patients [18-21].

It is clear that PET/CT provides us with additional information regarding size of the primary tumor and its relation to surrounding tissues. In considerable number of patients this examination reveals nodal involvement not identified by conventional methods [18,22].

Reduced target volumes may spare critical surrounding tissues and reduce adverse treatment reactions [22]. However, they may also lead to suboptimal disease control. A recently published case study described loco-regional recurrence of a parotid salivary gland primary tumor in 3 patients treated with IMRT [23]. In two cases the recurrence occurred in periparotic lymph nodes which appeared to be unaffected by the disease based on PET/CT examination. Whether it was due to a necrosis of affected lymph nodes or a limitation of the diagnostic technique itself is difficult to say. However, significant discrepancy between findings of conventional diagnostic methods and PET/CT should be always regarded as very suspicious and all such cases should be re-assessed using all available diagnostic methods [24].

It is estimated that primary location is not found in approximately 1–2% newly diagnosed head and neck metastatic tumors and a PET/CT examination may considerably contribute to their identification [25-27]. In our case, PET/CT located all 3 cases of primary tumors unidentified by conventional diagnostic methods.

PET/CT also plays an important role in identification of new metastases and it is recommended by numerous authors for ruling out distant metastases in uncertain cases. The distant metastases unidentified by conventional methods were found in 3 (5.7%) of our patients.

A combined PET and CT examination may be beneficial in follow-up setting for identification of early recurrences following IMRT [27]. Whether it will become a part of a routine assessment is to be seen.

A PET examination brings additional information about the tumor, such as a presence and localization of hypoxic areas and/or areas of increased proliferation. This can help us to target predominantly specific hypermetabolic areas as well as potentially radio-resistant hypoxic tumor areas suitable for IMRT treatment [28,29].

Conclusion

There is still no agreement on the role of PET/CT for radiotherapy planning in head and neck tumors. Evaluation of target volume remains the most important part of radiotherapy planning and a clinical examination together with CT remains the optimal standard. PET/CT gives us additional information about tumor size and structure which may, in some cases, help us to plan radiotherapy more precisely. Even PET/CT is unable to identify microscopic tumors and in many cases does not change the extent of prophylactic radiation. PET/CT allows us more precise evaluation of tumor size and definition; however, to what extent this improves the treatment outcomes and patients´ quality of life is unclear and will require further research.

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