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Can initial histopathological factors predict response to induction chemotherapy in advanced head and neck squamous cell carcinoma (HNSCC) - a comparison to 18-FDG-PET/CT

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1. Abstract

Objective: The treatment of advanced head and neck squamous cell carcinoma (HNSCC) with induction chemotherapy before radiation therapy has become more acknowledged over the last few years. The aim of our study was to find out, if histopathological parameters of the untreated primary tumor in HNSCC e.g. initial primary tumor grade, proliferation index, glucose transporter protein 1 (GLUT-1) expression could be possibly related to therapy response. Sequential 18F-FDG-PET/CT imaging before and after induction chemotherapy and resulting 18F-FDG-uptake was used as a surrogate for therapy response and compared to patient outcome.

Materials and Methods: 21 patients with advanced HNSCC treated by induction chemotherapy as first-line therapy were consecutively enrolled in this study. Defined responders (standardized uptake value (SUV) decrease > 75%) and non-responders (SUV decrease < 25%) were correlated to initial tumor grade (well, moderately, poorly differentiated) and other histopathological parameters including mitotic index, regression score and the expression of the GLUT-1 receptor for possible response predictive factors. Further, patient outcome was evaluated especially regarding survival.

Results: No significant correlation (p=0.472) could be found between response and histological grading (moderately or poorly differentiated). There was no significant difference between the SUV response and composition of chemotherapy (p=0.465), overall cycles (p=0.407), T-stage (p=0.557) or location of primary tumor (p=0.054). After a mean follow-up of 12 months, 6 patients were dead of disease, of which 5 had been classified as partial or non-responders and only one as a complete responder by 18F-FDG-PET/CT.

Conclusion: Since metabolic response was not correlated to initial histological parameters, response to chemotherapy can not be predicted by histopathological parameters alone. However, 18F-FDG-PET/CT seems to be a useful imaging protocol to monitor therapy response and may help to define therapy decision after induction chemotherapy.

2. Introduction

Carcinomas of the head and neck region represent 6.5% of the overall cancer incidents [1]. The majority of them (90%) are of squamous cell origin [1]. The common risk factors for developing head and neck squamous cell carcinoma (HNSCC) are the abuse of tobacco and alcoholic beverages. Men are more frequently affected than women, but the proportion of female patients has risen slightly due to the increased consumption of alcohol and tobacco among the latter group [2, 3].

The survival rate for patients with HNSCC (approximately 55% after 5 years) is still low even though various efforts have been undertaken to improve the outcome of HNSCC [1].

The treatment plan for patients suffering from HNSCC is a very demanding task; often discussed and planned on a multidisciplinary approach by a team of head and neck surgeons, radio-oncologists, medical oncologists, radiologists, nuclear physicians and pathologists.

Early stage disease is well treated by a single approach consisting of surgery or radiotherapy alone, whereas advanced stage disease often requires a multidisciplinary approach combining these modalities. Further, chemotherapy has gained importance over the last years and concurrent chemo-radiotherapy is standard of care, when a curative approach is chosen [1, 4, 5, 6].

Lately, the role of chemotherapy has even increased using the idea of an induction chemotherapy (mostly consisting of docetaxel, cisplatin and 5-fluorouracil – abbreviated DCF) which is applied in a neo-adjuvant setting before definitive therapy [7, 8, 9].

The motivation for this kind of treatment is based on the general idea, that if patients respond well to induction chemotherapy, systemic micrometastasis as well as the primary tumor volume will be significantly reduced before definitive locoregional therapy, possibly improving patient’s outcome. It is unclear and still under investigation whether a complete response of the tumor to induction therapy should lead to a reduction of the radiation doses and whether this has an impact on the planning of the following radiation therapy [10].

Positron emission tomography with 18F-fluoro-2-deoxy-D-glucose (18F-FDG-PET) in combination with computed tomography (CT) plays an important role at initial staging and re-staging after therapeutic interventions, since change in 18F-FDG-uptake has been positively correlated to therapy response [11, 12]. In a recent publication by Kikuchi et al. sequential 18F-FDG-PET/CT after induction chemotherapy has been shown to be predictive of histopathological response in patients with HNSCC [13]. Histopathological response is considered the gold-standard for therapy assessment, however observation of tumor changes by using imaging modalities such as CT or magnetic imaging (MRI) has been used for evaluating therapy response after induction chemotherapy and is well described previously [13, 14, 15, 16].

The aim of our study was to find out, if histopathological parameters of the untreated primary tumor in HNSCC e.g. initial primary tumor grade, proliferation index, glucose transporter protein 1 (GLUT-1) expression could be possibly related to therapy response. If the success of therapy could be predicted by these rather simple histological analyses, a personalized therapy could be established as well as harmful therapies omitted. 18F-FDG-PET/CT imaging has demonstrated the potential to determine non-invasively therapy response in several solid tumors including HNSCC [12]. In this study, sequential 18F-FDG-PET/CT imaging before and after induction chemo-therapy and resulting dynamics of 18F-FDG-uptake was used as a surrogate for therapy response. 18F-FDG-uptake in 18F-FDG-PET/CT can be objectively assessed by measurement by so called standard uptake values of 18F-FDG-avid lesions including the primary tumor and its metastases. Responders were defined as those having a standardized uptake value (SUV) decrease of greater than 75% whereas non-responders were defined as those having a SUV decrease less than 25%. Patient outcome was also determined regarding the hard end-point of alive or dead-of-disease. By this simplified approach a possible link to the success of induction treatment could be made, even though not proved since only post-therapeutic histological analysis of tumor tissue would be regarded as gold-standard.

3. Materials and Methods

3.1. Patients

In this retrospective analysis we selected patients from January 2007 to January 2010 suffering from advanced stage HNSCC and treated by induction chemotherapy treatment as the first step before further curative local treatment. As second inclusion criteria, all patients had to be initially staged and re-staged after induction chemotherapy by 18F-FDG-PET/CT. In a second step, only patients who were not pretreated, especially chemo-naïve were then selected for final analysis. Essentially, all patients were first staged at the Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Zurich, Switzerland. As an institutional policy 18F-FDG-PET/CT was only performed in advanced disease to rule out second primaries or distant metastases. Informed consent was waived according to local ethical committee policy.

The clinical characteristics of the 21 patients are shown in table 1. An oversight in table 2 shows for every patient the location and stage of the tumor, the performed therapies, the follow-up in months and whether they were alive or were dead of disease (DOD) at the end of the follow-up.

3.2. Induction chemotherapy

As for induction chemotherapy, standard treatment protocol consisted of docetaxel (Taxotere®), a taxoid which leads to the polymerisation of the tubuli to stable microtubuli and inhibits the depolymerisation thus leading to an interference during the mitosis; cisplatin which shows a cytotoxic effect as a result of interfering with the deoxyribonucleic acid (DNA) metabolism independent of the cell cycle; and 5-fluorouracil (5-FU), a pyrimidine analogue which interferes with the synthesis of nucleic acid. Docetaxel and cisplatin were given per infusion on day one of the treatment cycle, each in a dosage of 75 mg/m². 5-fluorouracil was given as a permanent infusion in a dosage of 750 mg/m² from day one to day five.

Patient related deviations from this treatment protocol were made when necessary (e.g., reduced dosages, replacement of cisplatin with carboplatin in patients with renal insufficiency).

Cetuximab (Erbitux®), a monoclonal IgG1-antibody which blocks the epithelial growth factor receptor (EGFR), was given in selected cases. This tyrosine kinase receptor stimulates cell proliferation, therefore it inhibits apoptosis and plays an important role in angiogenesis within the tumor. Cetuximab was given together with cisplatin or carboplatin and 5-FU. The dosage consisted of 400 mg/m² for the first cycle and 250 mg/m² for all the following cycles. Cisplatin was given in the dosage of 100mg/m² on day one; 5-FU as a permanent infusion in the dosage of 1000 mg/m² from day one to day four.

The dosage of the drugs which were used was as follows (sometimes slightly altered):
In the 'DCF' scheme one cycle consists of 75 mg/m² docetaxel and 75 mg/m² cisplatin on day one and 750 mg/m² 5-fluorouracil from day one to five. The cetuximab, 5-fluorouracil and carboplatin or cisplatin scheme consists of 400 mg/m² cetuximab on day one in the first cycle and for the following cycles 250 mg/m² cetuximab on day one, 100 mg/m² cisplatin on day one and 1000 mg/m² 5-fluoruracil from day one to four.
The details of the drugs used and the number of cycles of the induction chemotherapy are shown for each patient in table 3. This table also shows after how many cycles the 18F-FDG-PET/CT re-staging was done. The time gap between the last cycle before re-staging and the re-staging 18F-FDG-PET/CT was in most cases only a few days; all except one have been done within a span of two weeks. In one case the time gap was one and a half months due to health complications after the induction chemotherapy.

3.3. Imaging protocol

To complete the tumor staging and to evaluate its response to induction chemotherapy a 18F-FDG-PET/CT inline system (Discovery LS, RX or Discovery STE, GE Health Systems, Milwaukee, WI) was used. These devices combine a PET scanner with a multi-slice helical CT with a slice thickness of 2.5 mm, which enables the computation of coregistered PET and CT images in the same session.

Prior to scanning, patients had to fast for four hours at a minimum. Approximately sixty minutes before the scan, patients were given the injection of a standard dose of 350 megabecquerel (MBq) of 18F-FDG. Oral CT contrast agent (Micropaque Scanner, Guerbet AG, Aulnay-sous-bois, France) was applied a quarter of an hour before the injection of the 18F-FDG. Before scanning, all patients were tested for a normal glucose level (range 4.4 – 6.7 mmol/L). During their examination, patients were in a supine position and for the period of the CT scan they were instructed to hold their breath in the normal expiratory position. The acquisition of the PET emission scan followed immediately after the completion of the CT scan. The attenuation correction was acquired through the CT data and a standard iterative algorithm (OSEM: ordered set expectation maximization) was used for reconstructing the images for the 3D PET reconstruction. For viewing the acquired images a software providing multiplanar reformatted images of 18F-FDG-PET alone, CT alone and combined 18F-FDG-PET/CT with linked cursors was employed using an AW workstation (AW 4.4, GE Health Systems, Waukesha, WI, USA).

3.4. Analysis of 18F-FDG-PET/CT images

For a semiquantitative analysis of 18F-FDG uptake within the tumor tissue we measured the SUV_{max} over a freehand region of interest including the primary tumor site and cervical lymph node metastasis. For the correction of the SUV_{max} we used the lean body mass (LBM) of the patient, which was determined by a personal scale (Tanita, model 2001; Tanita, Tokyo, Japan). This model was supplied with an integrated foot-to-foot bioelectric impedance analyser. For the calculation of the LBM data on gender we used weight, height and a measured impedance value for the determination of the percentage of body fat. We determined the SUV_{max} by the following equation: $SUV_{max(LBM)}=(LBM - C_{FDG})/D$; C_{FDG} being the concentration of 18F-FDG in becquerels per milliliter, and D being the injected dose measured in becquerels. LBM was measured in grams.

To correct for physiological 18F-FDG uptake in this analysis, we measured the SUV of the bloodpool and substracted this value from the SUV_{max} of the tumor, in order to determine the absolute tumor SUV (SUV_{abs}).

In addition, the volume of the primary tumor was measured in cm^3 by using a 42% threshold of SUV_{max}. If cervical lymph node involvement was present, this volume

was added.

Regarding tumor response assessment, the following three parameters were chosen:

- Non-responder: a change of the SUV_{abs} of less than minus 25% of the initial value (SUV_{abs} from the pre-therapy 18F-FDG-PET/CT).
- Partial responder: a change of the SUV_{abs} between minus 25% and minus 75% of the initial value.
- Complete responder: a change of the SUV_{abs} of over minus 75% of the initial value.

3.5. Histopathological examination

All patients underwent a cytological or histological verification of the primary tumor and lymph node metastases before treatment. The cytological/histological specimens, respectively, were examined for the mitotic index and the GLUT-1 expression of tumor tissue, as well as the regression score which represents the proportion of the necrotic tumor cells within the tumor before treatment. To estimate the proliferation rate of a tumor, an immunohistochemical staining with MIB-1 was used, an antibody against Ki-67, which is a protein expressed in proliferating cells. Cells in mitosis are marked with MIB-1.

Tumor tissue was further examined for glucose transporter protein 1 (GLUT-1) expression, a transmembrane transport protein for both glucose and vitamin C, which shows a correlation to the malignancy of the tumor and represents an indicator for hypoxia within the tumor tissue [17, 18, 19].

Regarding GLUT-1 scoring, the following three parameters were chosen: score 0: 0% - 25%, score 1: 25% - 50%, score 2: 50% - 75%, score 3: 75% - 100%.

Regarding the tumor regression score, we examined samples with hematoxylin and eosin stain (HE stain) for vital and necrotic tumor cells, signs of surrounding inflammation and fibrotic reorganisation.

The tumor regression score from 0 to 2 depends on the proportion of vital tumor cells of the overall tumor tissue. The following three parameters were chosen: score 0: 0% - 10%, score 1: 10% - 50%, score 2: 50% - 100%.

Of the 21 patients, 3 patients had a biopsy or cytology sample taken before the initiation of induction chemotherapy which was not usable for our study. In 16 patients

biopsy samples and in 2 patients cytology samples were available for analysis. From all biopsy samples MIB score, GLUT-1 score and the tumor regression score were determined. From the cytology samples, MIB and GLUT-1 score were available.

3.6. Statistical analysis

We assessed the correlation between the SUV response and respectively the histological grading of the tumor, the induction chemotherapy scheme and the number of cycles, the primary tumor site and the TNM staging of the HNSCC. For statistical analysis, a Fisher exact test, especially eligible for small patient population, was used to determine the level of significance. A p-value < 0.05 was regarded as significant. All statistical analyses were performed using the SPSS 17 (SPSS Inc. Chicago, Illinois).

4. Results

4.1. Patients and tumor characteristics

From 2007 to 2010 251 patients underwent 18F-FDG-PET/CT for staging of advanced HNSCC. Of these, 56 had induction chemotherapy as initial treatment; 31 of them were restaged after induction chemotherapy by a second 18F-FDG-PET/CT. Twenty-five patients were not restaged by 18F-FDG-PET/CT for the following reasons: died of disease (n=10), or restaged by other imaging modalities (CT n=9; Magnetic Resonance Imaging (MRI) n=4). Furthermore, the treatment plan of one patient was changed after two cycles to a palliative scheme with methotrexate without an imaging technique for re-staging (n=1), and another patient needed to stop the induction chemotherapy after one cycle due to an aggravated thrombocythaemia (n=1).

In order to evaluate only pre-treatment-naïve patients, 10 out of the remaining 31 patients had to be excluded, since the actual treatment was a second-line therapy. Finally, 21 patients meeting our final selection criteria could be included. The details regarding tumor characteristics and the treatment scheme are shown in tables 1 and 2.

4.2. Induction chemotherapy

Out of the 21 included patients, 12 underwent the typical 'DCF' scheme consisting of docetaxel, cisplatin and 5-fluorouracil. 2 patients initially treated with cisplatin needed to be substituted by carboplatin due to hearing impairment or kidney dysfunction. Another group (6 patients) was treated with the combination of cetuximab, 5-fluorouracil and carboplatin or cisplatin. Only one patient received the combination of carboplatin and 5-fluorouracil without cetuximab as this patient worried about the possibility of skin problems. Details of chemotherapy schemes are shown in table 3.

4.3. Pathology results

The results are shown in table 5. Most patients showed poorly differentiated tumor cells. The MIB-1 score ranged from 10% to 80% with the majority of patients having a score of 40% or higher. Both of these histological parameters indicated a rather aggressive tumor. Most patients showed a GLUT score of 2 or 3 suggesting an advanced malignancy of the tumor, whereas the regression score was rather low, meaning that the majority of the tumor cells were vital.

4.4. Results of the 18F-FDG-PET/CT findings

The measured parameters SUV_{max}, tumor volume in cm^3, bloodpool and threshold of each patient are shown in table 4. The absolute SUV was calculated with the equation $SUV_{abs} = SUV_{max} – SUV_{bloodpool}$. Table 5 presents the change of the SUV_{abs} between the staging 18F-FDG-PET/CT and the re-staging 18F-FDG-PET/CT as well as the change of the tumor volume. The response to induction chemotherapy differed notably from patient to patient. In certain cases (e.g. patient 12), SUV was reduced to the level of $SUV_{bloodpool}$, resulting in an almost complete disappearance of the tumor, translating into a complete response. On the other hand, patient 1 revealed increased tumor uptake but inversely reduced tumor volume. Some patients showed no change at all after therapy. Overall, 6 patients were determined as non-responders, 7 as partial responders and 8 as complete responders (table 6). In the section “Figures” (chapter 8) the 18F-FDG-PET/CT findings of one patient are set out as an example of a complete responder (Fig. 1) and of another patient who exhibited no SUV change and an increase in the tumor volume as an example of a non-responder (Fig. 2). After a mean follow-up of 12 months, 6 patients were dead of disease, of which 5 had been classified as partial or non-responders and only 1 patient had been classified as a complete responder by 18F-FDG-PET/CT.

4.5. Statistical results

No significant correlation ($p=0.472$) could be established between the response of the patients and the histological grading. Further, there was no significant correlation between the response of SUV and the composition of the chemotherapy ($p=0.465$). No correlation between the response SUV and overall cycles ($p=0.407$) could be

shown, neither. Last but not least, there was no significant correlation between the response of SUV and T-stage or location of the primary tumor ($p=0.557$ and $p=0.054$, respectively). The latter comparison was able to show a statistical tendency towards the response of SUV and tumors arising from the hypopharynx.

5. Discussion

In our study, we were unable to identify a significant correlation between histopathological or therapeutic characteristics and the response, defined by 18F-FDG-uptake reduction in 18F-FDG-PET/CT imaging as a surrogate for response. However, reduction of 18F-FDG-uptake of 18F-FDG-PET/CT after induction chemotherapy seems to be related to patient outcome since a pronounced number of so called responders were still alive compared to non-responders.

The aim of our study was to find out, if histopathological parameters of the untreated primary tumor in HNSCC e.g. initial primary tumor grade, proliferation index, glucose transporter protein 1 (GLUT-1) expression could be possibly related to therapy response. Even if one of the histopathological parameters of untreated tissue would correlate to response or non-response, futile therapies could be omitted. This decision pathway is actually known in specific anti-body treatment in other solid tumors like bronchial carcinoma or colon cancer but not for HNSCC [20]. Since the common histopathological evaluation does not include highly sophisticated, gene-based analyses, a correlation was initially also not expected. Especially, in this study, no significant correlation regarding 18F-FDG-PET/CT response to histological factors like grade of differentiation, MIB-fraction or regression score could be found. Other studies could demonstrate, that p53 [21] as well as class III beta-tubulin [22] could be inversely correlated to progressive free survival and response rate to chemotherapy regimens also used in this study. For this study, these known factors could not be analyzed due to the retrospective nature of the data.

We defined the responders and non-responders by means of the SUV change in the 18F-FDG-PET/CT examinations because in general, reduction of 18F-FDG-uptake in 18F-FDG-PET and 18F-FDG-PET/CT imaging after any intervention in oncological as well as inflammatory disease is regarded as response and possibly correlates with disease outcome. The probably best studied disease regarding therapy response assessment is lymphoma [23]. Here, reduction and normalization of 18F-FDG-uptake in treated lymphoma has been significantly correlated to progression free survival [24]. For solid tumors similar results could be demonstrated as for example in esophageal cancer [25].

The use of 18F-FDG-PET and 18F-FDG-PET/CT imaging in the evaluation of HNSCC is well established, since squamous cell carcinoma also demonstrate a high avidity in 18F-FDG-uptake and allows for the correct staging of this type of tumor [26, 27]. Regarding therapy evaluation after completion of radio-chemotherapy in a curative intent, a high negative predictive value has been demonstrated [28]. Relatively few data has been published regarding the use of 18F-FDG-PET/CT in the evaluation of therapy response assessment in advanced HNSCC treated by induction chemotherapy, since this treatment is a relatively new approach in the curative setting. In a study by Kikuchi et al., histopathological response as gold-standard was compared to 18F-FDG-PET/CT- and MRI responses since all 16 included patients were surgically treated after induction chemotherapy with available histological specimens [13]. Using a threshold of 55.5% reduction in SUV_{max}, histopathological response could be predicted with a sensitivity of 86% and specificity of 95%. These results strongly underline not to say prove our working hypothesis that reduction in SUV of more than 75% was correlated to histopathological response, since we had no access to post-chemotherapy histology and the majority of our patients were treated by non-surgical treatment. The problem of not having surgical specimens available after induction chemotherapy is due to the concept of organ-preservation therapy; therefore imaging modalities for monitoring therapy response after induction chemotherapy seem to be a useful method. Having a look at our 18F-FDG-PET/CT-related results for response, 8 patients showed a complete response (reduction of SUV_{abs} > 75%); 7 patients a partial response and 6 patients showed no response at all. Therefore, less than 50% demonstrated a complete metabolic response.

In summary, we observed a large variation in the response to induction chemotherapy; however, we could not identify a single factor which might explain that difference. For example, there was no significant correlation (p=0.472) between response and histological grading. Further, there was no significant difference between the SUV response and the composition of the chemotherapy (p=0.465) as well as the correlation to the overall number of chemotherapy cycles (p=0.407). No significant correlation was identified between SUV response and T-stage (p=0.557) nor between SUV response and location of primary tumor (p=0.054). As a certain clinical surrogate for response, we used the clinical follow-up. The mean follow-up in our patient population was 11.1 months which seems to be sufficiently long, since

early recurrence or persistence of disease occurs mostly within the first six months. Interestingly, 6 patients died of disease, of whom 2 were classified as non-responders, 3 as partial responders and 1 as a complete responder. Therefore, response to induction chemotherapy before definite curative treatment shows a positive effect on outcome, which is obviously the general purpose of this treatment. Therefore, response to treatment can be determined in a non-invasive manner using sequential 18F-FDG-PET/CT imaging. The translation of these findings into clinical routine seems on the one hand straightforward, however, on the other hand, how should patients be treated, who were re-staged as so called non- or partial responders? Obviously one cannot conclude that further treatment should be withdrawn, because the remaining 15 patients continued to survive, regardless of their classification as complete, partial or non-responders.

A limitation of this study is the small patient population of 21 patients whom we examined. In our limited sample instances of moderately differentiated tumor tissue are underrepresented (7 out of 21 cases) compared to 14 instances of poorly differentiated tumor. With a small number of patients it is difficult to derive statistically significant values.

In conclusion, none of the histological parameters we examined (histological grading, MIB score, GLUT-1 score, regression score), are able to serve as an indicator before induction therapy as to whether a patient could likely benefit. However, the 18F-FDG-PET/CT findings show a wide discrepancy in SUV response as well as the change of the tumor volumes between patients. This is important information for making further efforts to find a way to improve the criteria for determining which patients should be treated by induction chemotherapy. A further search for certain tumor characteristics which could have an influence on the outcome of induction chemotherapy will be an important field for future research. For example, the examination of HNSCC which are positive for human papillomavirus (HPV) may react differently than those which are HPV negative. This could be of importance, since the proportion of HNSCC that has been tested HPV positive has risen during the last few years.

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7. Tables

Table 1. Clinical characteristics of the 21 patients with induction chemotherapy as first line therapy

Women	2	9.5%
Men	19	90.5%
Age (years)		
Mean	57.1	
Range	42-75	
Location of primary HNSCC		
Oral cavity	2	9.5%
Oropharynx	5	23.8%
Hypopharynx	9	42.9%
Larynx	2	9.5%
Epipharynx	1	4.8%
Other	1	4.8%
Unknown	1	4.8%
Induction chemotherapy		
T/C/F	12	57.1%
CB/F/E	3	14.3%
C/F/E	3	14.3%
T/CB/F	2	9.5%
CB/F	1	4.8%

The proportion refers to the total of 21 patients, Abbreviations: C: cisplatin CB: carboplatin E: Erbitux® (cetuximab), F: 5-fluorouracil, T: Taxotere® (docetaxel)

Table 2. Details of 21 patients with induction chemotherapy followed by a re-staging with PET/CT

Patient No.	Gender	Age	Location of primary tumor	TNM stage	Histological grading	First-line therapy	Second-line therapies	Follow-up (months)	DOD
1	m	63	larynx	T3 N3 M0	moderately differentiated	cur-Ind	RT/C, ND[2], C	12	no
2	m	52	hypopharynx	T4b N2 Mx	moderately differentiated	cur-Ind	RT/C	5	no
3[o]	m	52	oral cavity	T4 N0 Mx	poorly differentiated	cur-Ind		5	yes
4[1]	m	53	hypopharynx	T4 N0 M0	moderately differentiated	cur-Ind		13	no
5	m	64	epipharynx	T4 N0 Mx	moderately differentiated	cur-Ind		1	yes
6	m	64	oropharynx	T4 N2 M0	poorly differentiated	cur-Ind	RT/C, salvage-ND	7	no
7	m	55	oropharynx	T4 N2 M1	moderately differentiated	cur-Ind	RT/C, C	11	yes
8	m	75	larynx	T4 N0 Mx	poorly differentiated	cur-Ind	RT/C	5	yes
9	m	42	other	T3 N2 Mx	poorly differentiated	cur-Ind		1	no
10	m	62	hypopharynx	T4 N3 M1	moderately differentiated	cur-Ind	RT/C	21	no
11	m	55	unknown	T0 N3 M1	poorly differentiated	cur-Ind	RT/C, ND	14	no
12	m	46	oropharynx	T4 N2b M0	poorly differentiated	cur-Ind	RT/C	22	no
13	m	68	hypopharynx	T4 N2 M0	moderately differentiated	cur-Ind	RT/C, Resection[3]	9	no
14	m	47	hypopharynx	T1 N3 M0	poorly differentiated	cur-Ind	RT/C, ND[2]	31	no
15	m	44	oral cavity	T2 N0 M0	poorly differentiated	Resection	RT/C, cur-Ind	10	yes
16	m	48	hypopharynx	T3 N3 M0	poorly differentiated	cur-Ind	RT/C, salvage-ND	14	no
17	m	54	hypopharynx	T2 N2c M1	poorly differentiated	cur-Ind	C	9	no
18	m	52	hypopharynx	T2 N2b M0	poorly differentiated	cur-Ind	RT/C, ND	32	no
19	f	68	unknown	T0 N2b M1	poorly differentiated	p-Ind	C	7	yes
20	m	66	oropharynx	T4b N2 M0	poorly differentiated	cur-Ind	RT/C	7	no
21	f	70	oropharynx	T2 N0 M0	poorly differentiated	cur-Ind	C	17	no

[o]:This patient had 8 years prior to current diagnosis surgery and RT because of another HNSCC

[1]:This patient had 8 years prior to current diagnosis induction chemotherapy and RT/C because of another HNSCC

[2] : because of persisting lymph node Metastasis, [3]: transoral laser resection because of persisting primary tumor, Abbreviations: ND: neck dissection,

RT/C: concomittant radiochemotherapy, p-Ind: palliative induction chemotherapy, cur-Ind: curative induction chemotherapy, C: chemotherapy, DOD: dead of disease

Table 3. Details about the induction chemotherapy of all 21 patients with a PET/CT for re-staging

Patient No.	Induction chemotherapy	Overall cycles	Re-staging PET/CT[1]
1	CB/F/E	3	3
2	T/C/F	3	2
3	T/C/F	6	3
4	T/C/F	5	3
5	T/CB/F	3	3
6	T/CB/F	3	3
7	C/F/E	6	3
8	CB/F/E	3	3
9	T/C/F	3	2
10	T/C/F	3	3
11	T/C/F	3	3
12	T/C/F	4	4
13	T/C/F	4	4
14	T/C/F	3	3
15	C/F/E	6	3
16	T/C/F	3	3
17	CB/F	4	3
18	T/C/F	4	4
19	CB/F/E	3	3
20	T/C/F	3	2
21	C/F/E	4	3

[1]: This column shows after how many cycles the PET/CT was done for re-staging
Abbreviations: C: cisplatin, CB: carboplatin, E: Erbitux® (cetuximab), F: 5-fluorouracil, T: Taxotere® (docetaxel)

Table 4. SUVmax, tumor volume in cm3, bloodpool and threshold of the 21 patients with induction chemotherapy as first-line treatment

Patient No.	SUVmax PET/CT 1	Tumor volume PET/CT 1[1]	Bloodpool PET/CT 1	Threshold PET/CT 1	SUVmax PET/CT 2	Tumor volume PET/CT 2[1]	Bloodpool PET/CT 2	Threshold PET/CT 2
1	5.4	130	1.7	31	7.8	45	2.2	28
2	15.9	126	2.4	15	5.4	37	2.3	43
3	16.8	18	3	18	9.8	16	2.7	28
4	11.5	23	2.4	21	11.7	27	2.4	21
5	13.4	163	3.1	23	13.5	350	3.2	23
6	12.3	133	2.3	19	4.7	23	2.1	45
7	15.1	155	2.2	15	3.4	15	2.2	65
8	8.9	158	1.7	19	10.7	139	2.7	25
9	9	134	2.3	25	10.1	59	2.2	21
10	10.4	28	2.6	25	3.1	6	2.4	77
11	12.9	92	2	17	3.6	3	2.5	70
12	23.8	188	2.9	12	3	4	2.5	83
13	7.8	76	3	38	6	6	2.9	48
14	20.7	156	1.8	9	2.8	5	1.9	62
15	7.4	72	2.2	30	3.3	26	1.8	55
16	21.6	72	2.7	13	9.9	10	2.6	26
17	10.3	137	2.1	20	5.9	36	2.2	37
18	12.3	75	2.3	19	3.4	6	2.1	62
19	5.1	75	1.9	37	4.6	9	2.3	50
20	10.1	134	2.8	28	4	3	2.5	62
21	6.8	53	2.4	35	15.2	40	2.3	15

[1]: Tumor volume includes the volume of the primary tumor plus the volume of the cervical lymph node metastasis, Abbreviations: PET/CT 1: PET/CT for staging, PET/CT 2: PET/CT for re-staging

Table 5. Tumor response in PET/CT and the pathological characteristics of the 21 patients with induction chemotherapy as first-line therapy

Patient No.	SUVabs change between first and second PET/CT	SUVabs change in %[2]	Change of tumor volume in cm³ between first and second PET/CT[1]	Change of tumor volume in %[2]	Histological grading	MIB score	GLUT-1 score	Tumor regression score
1	1.9	51.4%	-85	-65.4%	moderately differentiated	40%	2	1
2	-10.4	-77.0%	-89	-70.6%	moderately differentiated	70%	3	1
3	-6.7	-48.6%	-2	-11.1%	poorly differentiated	20%	2	0
4	0.2	2.2%	4	17.4%	moderately differentiated	70%	3	0
5	0	0.0%	187	114.7%	moderately differentiated	40%	2	1
6	-7.4	-74.0%	-110	-82.7%	poorly differentiated	60%	1	1
7	-11.7	-90.7%	-140	-90.3%	moderately differentiated	40%	2	0
8	0.8	11.1%	-19	-12.0%	poorly differentiated	n.m.	n.m.	n.m.
9	1.2	17.9%	-75	-56.0%	poorly differentiated	50%	1	n.m.
10	-7.1	-91.0%	-22	-78.6%	moderately differentiated	30%	2	1
11	-9.8	-89.9%	-89	-96.7%	poorly differentiated	n.m.	n.m.	n.m.
12	-20.4	-97.6%	-184	-97.9%	poorly differentiated	50%	3	0
13	-1.7	-35.4%	-70	-92.1%	moderately differentiated	60%	3	0
14	-18	-95.2%	-151	-96.8%	poorly differentiated	70%	2	1
15	-3.7	-71.2%	-46	-63.9%	poorly differentiated	50%	1	2
16	-11.6	-61.4%	-62	-86.1%	poorly differentiated	60%	2	1
17	-4.5	-54.9%	-101	-73.7%	poorly differentiated	n.m.	n.m.	n.m.
18	-8.7	-87.0%	-69	-92.0%	poorly differentiated	40%	3	0
19	-0.9	-28.1%	-66	-88.0%	poorly differentiated	10%	2	n.m.
20	-5.8	-79.5%	-131	-97.8%	poorly differentiated	80%	3	0
21	8.5	193.2%	-13	-24.5%	poorly differentiated	80%	3	0

[1]: Tumor volume includes the volume of the primary tumor plus the volume of the cervical lymph node metastasis, [2]: First PET/CT measure data as output value
Abbreviations: SUVabs: absolute standardized uptake value, PET/CT: 18F-FDG positron emission tomography combined with computed tomography, n.m.: not measurable

Table 6. Number of responder, non-responder and partial responder

	Number of patients:	Percentage of the total 21 patients:
Complete responder:	8	38.1%
Non-responder:	6	28.6%
Partial responder:	7	33.3%
Total patients:	21	100.0%

Responder: a change of the SUV $_{abs}$ of over minus 75% of the initial value
Non-responder: a change of the SUVabs of less than minus 25% of the initial value
Partial responder: a change of the SUVabs of between minus 25% and minus 75% of the initial value

8. Figures

(Fig. 1) 46-year-old patient with a poorly differentiated HNSCC of the oropharynx, diagnosed one month before the pre-induction chemotherapy 18F-FDG-PET/CT. Lower row from left to right: axial fused PET/CT, axial PET, and maximum intensity projection (MIP) of PET data; primary tumor at the level of the oropharynx with infiltration of the right parapharyngeal space. Upper row, left to right: axial PET/CT, axial PET and MIP of PET after 4 cycles of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil the post-induction chemotherapy 18F-FDG-PET/CT shows a complete response (SUV of the tumor region is the same as the SUV of the bloodpool).

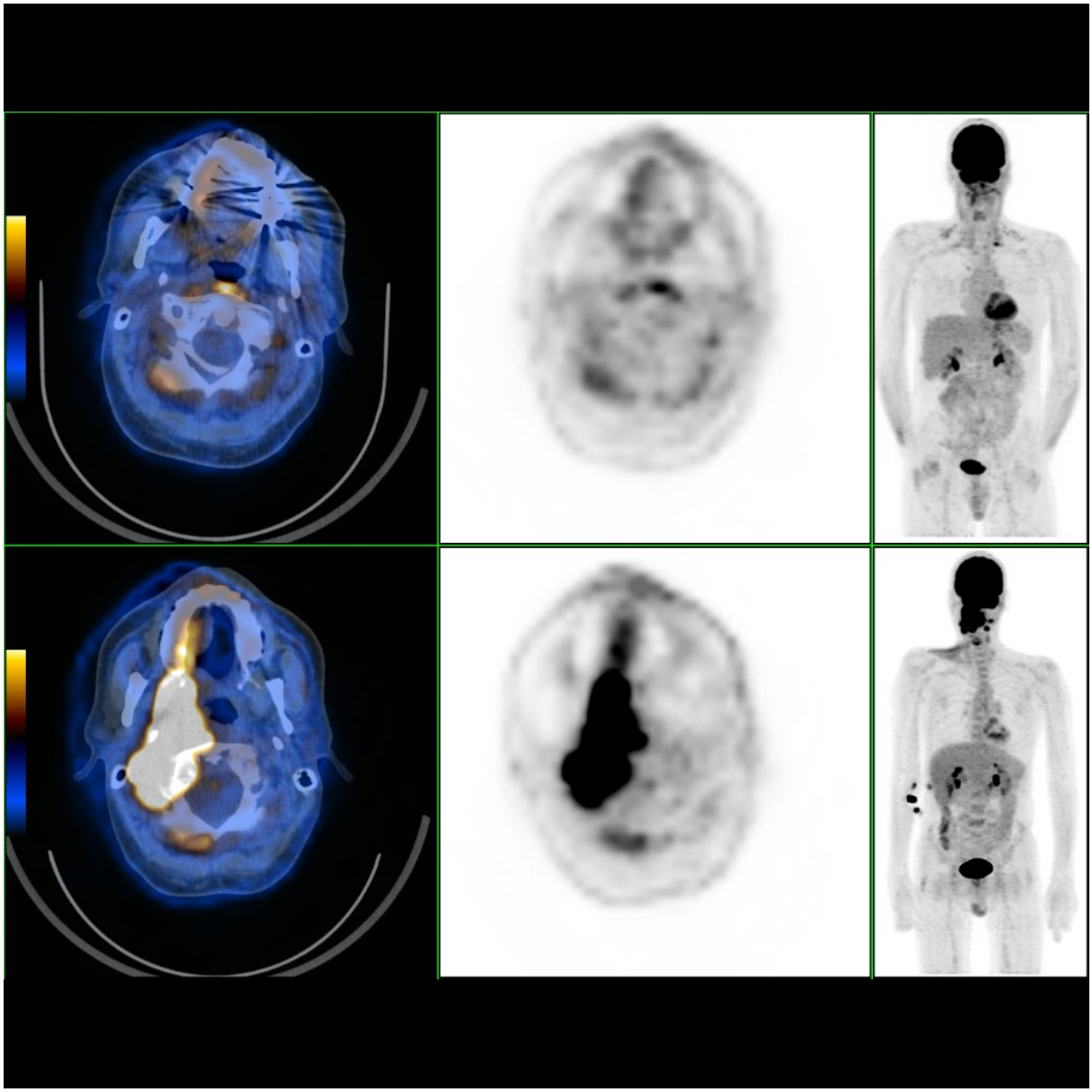

Figure 1

(Fig. 2) 64-year old patient with a poorly differentiated HNSCC of the maxillary of the right side. Lower row from left to right: axial fused PET/CT, axial PET, and maximum intensity projection (MIP) of PET data; primary tumor at the level of the right maxillary ridge with infiltration of the soft and hard palate and bilateral lymph node metastases. Upper row, left to right: axial PET/CT, axial PET and MIP of PET after 3 cycles of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil shows extensive progression with infiltration of the right as well left parapharyngeal space.

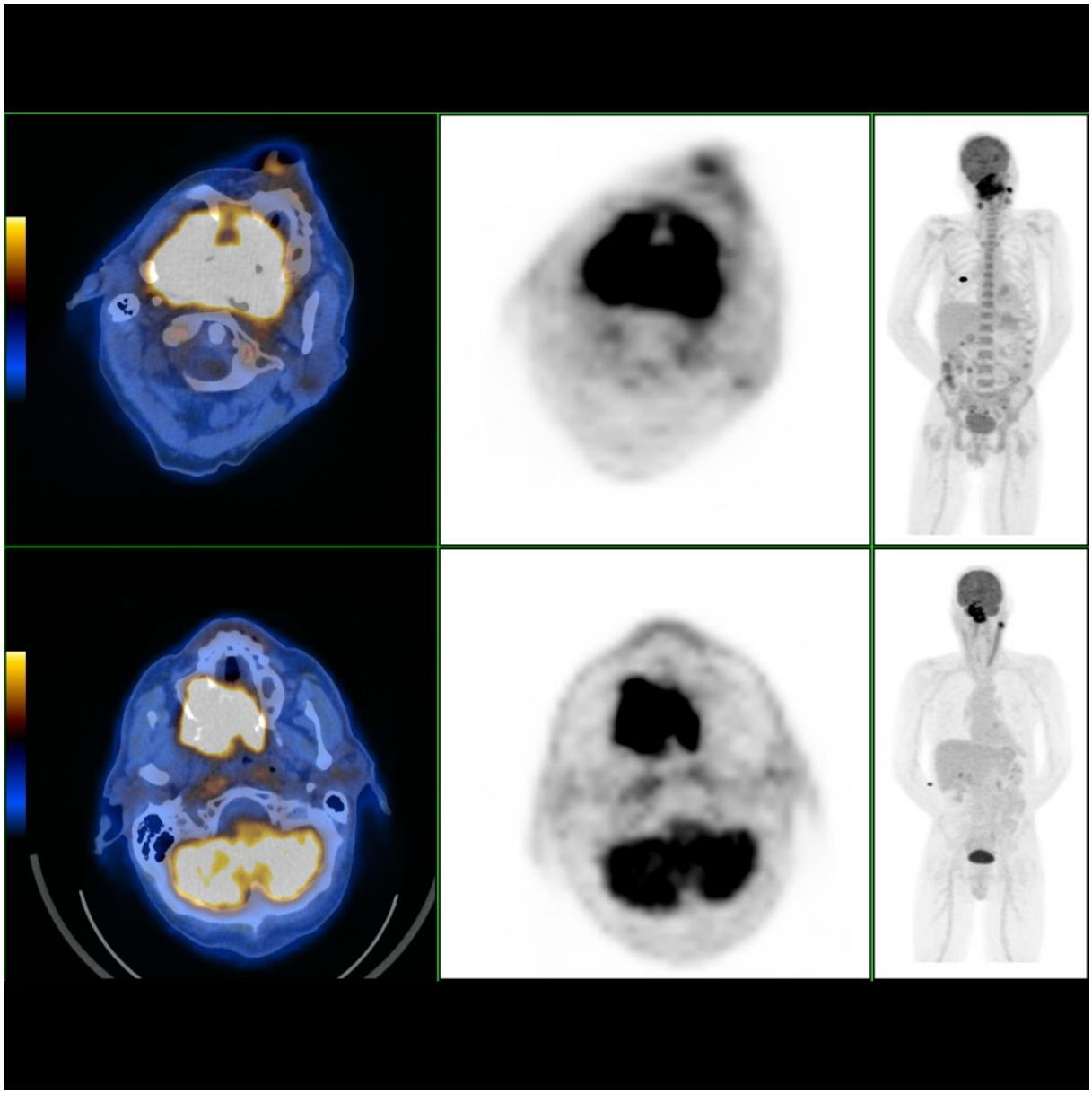

Figure 2

9. Acknowledgments

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10. Curriculum Vitae

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1996 – 2002	Langzeitgymnasium Kantonsschule Rychenberg, Winterthur mit Englisch als Schwerpunkt- und Latein als Grundlagefach
2003 – 2009	Medizinstudium an der Universität Zürich
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