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Impact of pretreatment second look ^{18}FDG-PET/CT on stage and treatment changes in head and neck cancer

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ABSTRACT

Background: Patients diagnosed with locoregionally advanced head and neck squamous cell carcinoma (LAHNSCC) regularly undergo staging with ^{18}F-FDG PET/CT in our center. In cases of delays in radiotherapy (RT) planning CT more than 4 weeks after initial PET/CT or clinically suspected progress, PET/CT is repeated for restaging and as an RT planning reference. Our aim was to determine the impact of second-look PET/CT on stage migration, treatment change and RT planning.

Methods: Consequent treatment changes were categorized as minor and major. Minor changes were defined as PET/CT-based modifications of RT plans, e.g., the addition of anatomical compartments, changes in high- and low-risk dose levels or both. Major changes included changes from curative to palliative treatment intent and alterations of interdisciplinary treatment plans, such as the addition of induction chemotherapy, switch to primary surgery, no treatment and/or the necessity of additional diagnostic work-up resulting in the postponement or cancellation of treatment.

Results: Thirty-two newly diagnosed LAHNSCC patients who were treated between 2014 and 2018 underwent second-look PET/CT (median interval 42.5 days). Second-look PET/CT led to locoregional and distant upstaging in 3/32 and 1/32 patients, respectively. In 1/32 patients (3%), second-look PET/CT led to a palliative approach with systemic treatment. New lymph node metastases were discovered in 16 patients, 6 of whom also showed significant progression of the primary tumor, resulting in minor changes in 16 of the remaining 31 patients (52%) who were treated curatively.

Conclusion: If RT treatment planning of LAHNSCC was delayed by more than 4 weeks after initial PET/CT staging or when progression was clinically suspected, a second look at ^{18}FDG-PET/CT was performed. This led to changes in treatment planning in more than half of the cases, which is expected to directly influence oncologic outcomes.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common malignancy worldwide, and most patients require radiotherapy (RT) as part of a single- or multimodal treatment concept [1–3]. Patients with locoregionally advanced HNSCC (LAHNSCC) diagnosed in our center undergo initial tumor staging with integrated ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT) as part of the diagnostic work-up [4] before multidisciplinary tumor board presentation. If the RT planning CT is performed 4 weeks or more after the initial PET/CT due to logistic, medical and/or patient-related factors or in case of clinical suspicion for tumor progression, the PET/CT exam is repeated in the RT position. The underlying reason for such repeated PET/CT imaging is the aggressive biology and high dynamics of HNSCC, with a risk of upstaging in the interval due to locoregional and/or systemic progression [5,6]. Finally, our hope is to improve the RT planning accuracy, having up-to-date image information of the current tumor extent available. At our

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institution, additional, parallel repeated magnetic resonance imaging (MRI) is usually omitted due to financial and logistical reasons. This practice was established as a standard in our center in 2014. The aim of this retrospective study was to determine the impact of second-look PET/CT on RT planning and changes in treatment indications.

Methods and materials

A retrospective chart and plan review of eligible patients who were diagnosed with two pretreatment PET/CTs and treated between 2014 and 2018 was performed. Eligibility criteria were ≥ 18 years of age; histopathologically proven LAHNSCC of the oral cavity, oropharynx, larynx or hypopharynx in stages III-IVB (Union for International Cancer Control 7th edition); treatment indication for definitive RT (normofractionated with concomitant chemotherapy or hyperfractionated); no induction chemotherapy or primary surgery; and no previous radiation to the neck.

All patients kept a carbohydrate-free diet for at least 6 h before the PET/CT examination, and the blood glucose level was below 10 mmol/L before intravenous injection of 4–5 MBq ^{18}F-fluorodeoxyglucose (FDG)/kg body weight. PET/CT was performed with a standardized acquisition protocol using an integrated PET/CT system (Biograph mCT 128 True V, Siemens Medical Solutions, Germany). Emission images of the trunk (neck to the pelvis) were obtained 90 min after injection (5–7 bed positions, 2 min per bed position) followed by dedicated high-resolution PET acquisition of the head and neck region (1 bed position, axial coverage 21.6 cm, 10 min per bed position). All PET images were reconstructed using an iterative time-of-flight algorithm including point spread function correction (TrueX). PET images of the trunk were reconstructed with a matrix size of 200x200, 5 mm Gauss filtering and a voxel size of 4 mm. High-resolution PET images of the head and neck region were reconstructed with a matrix size of 512x512, 2 mm Gauss filtering and a voxel size of 1.6 mm. PET images were coregistered with a low-dose CT (120 kV, 80 mAs, reconstructed slice thickness 2 mm), which was also used for attenuation correction. In addition, all qualifying patients underwent an additional contrast-enhanced CT of the head and neck region (120 kV, 160 mAs, reconstructed slice thickness 2 mm).

In routine clinical practice, all PET/CTs were reviewed and reported by two board-certified physicians with more than 10 years of practice in oncological PET and PET/CT. The classification of lesions with FDG uptake as benign vs. malignant lesions was based on the integrated interpretation of metabolic (e.g., focal uptake, relative uptake intensity of primary tumor and possible metastatic lesions with respect to size-dependent partial-volume effects, activity distribution) and morphologic imaging criteria (e.g., size and shape of lesions, infiltration of surrounding tissues, necrosis, extracapsular extension).

Changes in the primary tumor, lymphatic spread and presence of distant metastases between two PET/CTs were extracted from the written original clinical reports. PET/CT-based treatment changes were categorized as minor and major treatment changes. Minor changes were defined as modifications of RT plans, e.g., the addition of anatomical compartments, the regional adjustment of dose levels or both. Major changes from curative to palliative treatment intent and alterations of interdisciplinary treatment plans included the addition of induction chemotherapy, switch to primary surgery, no treatment and/or the necessity of additional diagnostic work-up resulting in the postponement or cancellation of treatment.

Minor and major changes were evaluated on a case-by-case basis and reported categorically. The predictive value of the time interval between two PET/CTs for such changes in treatment was analyzed with logistic regression. Metabolic tumor volume (MTV) for the primary tumor and involved lymph nodes was calculated based on the externally validated method defined by Castelli et al. [7]. MTV was determined based on relative thresholds of 35% mean standard uptake value (SUVmean) for primary tumors and 44% for lymph nodes. These thresholds were reported with their high prognostic value regarding overall survival. JMP (version 14.0; SAS Institute, Germany) was used for statistical analyses.

Results

Thirty-two newly diagnosed LAHNSCC patients who were treated between 2014 and 2018 underwent a second look PET/CT for restaging and RT planning. Patient and tumor characteristics are provided in Table 1. The median interval between the staging and second look PET/CT examinations was 42.5 days (interquartile range: 35.25–55; range: 16–114). Two patients underwent a second-look PET/CT in <4 weeks due to clinical suspicion of tumor progression. The reason for the >4-week delay varied from logistic (i.e., regarding appointment scheduling), medical (need for further work-up) or patient-related factors. However, it was not completely possible to retrospectively reconstruct the exact reasons for delay.

Major treatment change occurred in 1/32 cases. The patient was diagnosed with new distant metastases after an interval of 66 days between both examinations and had undergone upfront neck dissection for an N3 lymph node conglomerate in this time period. PET/CT findings finally led to a palliative approach with systemic treatment instead of initially planned radiochemotherapy. Of the remaining 31 patients, 3 underwent upfront neck dissection between two PET/CTs, and the change in their nodal status was disregarded for the analyses of nodal stage migration or treatment changes. Second look PET/CT led to nodal upstaging in 3/29 (10%) cases. Nodal upstaging accounted for stage migration as cN1 → cN2b (75 days between both PET/CTs), cN2b → cN2c (40 days) and cN0 → cN2b (43 days). None of the two patients who underwent the second-look PET/CT earlier than 4 weeks (16 and 22 days) due to clinical suspicion of progress were categorized as minor or major treatment changes.

Among the 31 cases continuing with curative treatment, minor treatment changes occurred in 16/31 (52%) patients. New lymph node metastases were detected in all 16 cases, of which 6 also showed evident progression of the primary tumor size without changes in cT stage. The numbers of new lymph nodes (number of corresponding cases) were 1 (n = 8), 2 (n = 4), 3 (n = 1), 5 (n = 2) and 6 (n = 1). The numbers of newly involved lymphatic levels [8] (number of corresponding cases)

Table 1
Initial patient and tumor characteristics.

Parameter	Distribution
Median age (range)	64 (27–83)
Female/male	11 (34%)/21 (66%)
Tumor subsite	
Oral cavity	9 (28%)
Oropharynx (HPV−)	12 (38%)
Oropharynx (HPV +)	4 (13%)
Larynx	3 (9%)
Hypopharynx	4 (13%)
Grade	
2	17 (53%)
3	13 (41%)
X	2 (6%)
cT stage*	
2	7 (22%)
3	10 (31%)
4a	14 (44%)
4b	1 (3%)
cN stage*	
0	5 (16%)
1	3 (9%)
2b	9 (28%)
2c	14 (44%)
3	1 (3%)

HPV: human papillomavirus association.
* staging according to the Union for International Cancer Control, 7th edition.

were 1 (n = 2), 2 (n = 4), 3 (n = 1), 4 (n = 1) and 5 (n = 1). The mean increase in the primary tumor MTV and the sum of involved lymph nodes were 6.7 cm^3 (range: −2.5 – 116.5 cm^3) and 2.80 cm^3 (range: −4.3 – 50.7 cm^3), respectively (Fig. 1). Modifications of the initially intended RT volumes and changes in involved lymphatic levels are summarized in Table 2. Images of an example case are demonstrated in Fig. 2.

The time interval between two PET/CTs was not predictive of the occurrence of any treatment change (R^2: 0.002; p = 0.768).

Discussion

To the best of our knowledge, this is the first study to investigate the value of a second-look PET/CT on stage migration and changes in treatment prior to definitive radiochemotherapy for LAHNSCC. Despite already benefitting from an initial PET/CT examination in terms of staging, minor treatment changes were necessary in more than half of the cases after the second look PET/CT. Regional and distant upstaging were seen in 10% and 3%, respectively. Half of the patients were diagnosed with newly involved lymph nodes, and one-third of the patients with additional lymphatic levels presented regional metastases. This led to substantial changes in the RT-plans. Interestingly, no predictive value of the time interval between two PET/CTs for treatment change was observed, which is likely due to the limited sample size. Therefore, it is not possible to define an optimal time threshold to recommend a second PET/CT after a given delay. It is also worth noting that no upstaging occurred in cT staging, although the volume increase of the primary tumors was greater than the volume increase of the sum of the involved lymph nodes with the missing values of the patients who underwent upfront neck dissection (6.7 cm^3 vs. 2.80 cm^3 on average, respectively). Another observation was that there seemed to be no clear correlation between the MTV changes and the emergence of newly involved lymph nodes. Moreover, some total MTV volumes even decreased despite the newly detected involved lymph nodes. This indicates that even the use of identical SUV thresholds on paired images with the same acquisition protocols may still yield such deviations.

The use of ^{18}FDG-PET/CT is considered a part of the initial investigations of LAHNSCC in the international guidelines for HNSCC [2,3] regarding the possibility of stage migration or in case of a carcinoma of an unknown primary. In our center, it is an integral part of primary staging prior to surgery or RT along with physical examination, panendoscopy under general anesthesia and MRI for LAHNSCC. RT planning is based on the integrated findings of all these examinations. Both MRI and PET/CT are fused with the contrast-enhanced simulation CT. Despite the superior anatomical resolution and soft-tissue contrast of MRI, PET/CT is repeated in cases of delays between the initial imaging and the simulation CT. Unfortunately, it is not financially possible to repeat both imaging modalities. We prefer to scan the whole body for possible distant metastases through PET/CT followed by dedicated high-resolution PET acquisition of the head and neck region. Additionally, MRI is substantially hampered by dental artifacts, which is quite relevant for the visualization of the oral cavity and some oropharyngeal tumors. Moreover, according to our experience, dedicated high-resolution PET/CT of the head and neck region appears at least non-inferior or even superior to MRI and CT for the detection of pathologically involved lymph nodes and distant metastases and helps to detect second primary malignancies [9,10,19,11–18]. On the other hand, the anatomical resolution, tissue contrast and availability of different functional imaging sequences make MRI the superior modality for the identification and demarcation of primary tumors [20].

Until now, some studies have investigated the impact of PET or PET/CT on clinical decision-making. Generally, approximately 30% of the original treatment decisions may be amended with the addition of PET [21–24]. In a recent study, PET/CT led to changes in nodal RT volumes in 10% of the study population (n = 60). Most detected occult nodal metastases on initially cN0 necks (26%) were of those with oral cavity tumors [25]. The cost-effectiveness of PET/CT for the initial staging of HNSCC was demonstrated, including but not limited to cN0 stage, which is reported to be approximately $2500 per quality-adjusted life-year [26–28]. The phase III PET-NECK trial also demonstrated the feasibility and cost-effectiveness of PET/CT in response evaluation after radiochemotherapy [29].

Our cohort only consisted of LAHNSCC cases without any stage I-II tumors. It might be expected that early-stage tumors would benefit less

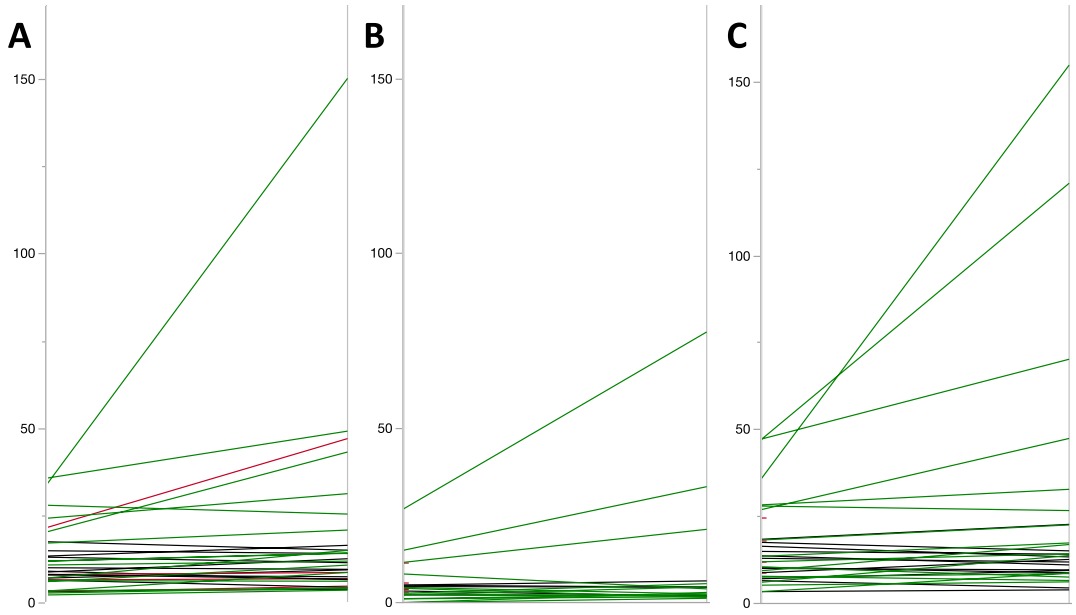

Fig. 1. Changes in primary tumor MTV, sum of involved nodes MTV and sum of all MTVs **Description of** Fig. 1**: A**: Primary tumor MTVs. **B**: Sum of the involved node MTVs. **C**: Sum of both MTVs. Each left Y-axis indicates the MTVs on the first PET/CTs, and the right side indicates the MTVs on the second PET/CTs in cc. Black lines correspond to the cases without any minor or major changes. The green lines and the red line represent the patients with minor and major changes, respectively. The four small red dashes on the left-hand Y-axes of Panels B and C indicate the patients who underwent upfront neck dissection after the first PET/CT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Individual tumor characteristics at the time of first and second PET/CT.

Patient	cT	cN	Anatomical subsite and Grade	Involved nodal levels (PET/CT-1)	Involved nodal levels (PET/CT-2)	cT MTV difference (cc)	cN MTV difference (cc)	Treatment Change	Complete miss?*
1	T3	cN3	Hypopharynx Grade 3	R: II, II, IVA L: -	UFND	1.7	UFND	cM1 → major	Not applicable
2	T3	N0	Oropharynx HPV- Grade 2	R: - L: -	R: - L: -	−0.8	0	no	no
3	T3	N2c	Larynx Grade 2	R: II, Vc L: Ib, II, III, Vc	R: II, Vc L: Ib, II, III, Vc	−1.6	−1.5	no	no
4	T3	N2c	Larynx Grade 2	R: I, II, III, IVA L: II, III	R: I, II, III, IVA L: II, III	3.8	<0.1	no	no
5	T3	N0	Oral cavity Grade 2	R: - L: -	R: - L: -	0.5	0	no	no
6	T4a	N0	Oropharynx HPV+ Grade 2	R: - L: -	R: - L: -	−0.4	0	no	no
7	T3	N0	Hypopharynx Grade 3	R: - L: -	R: - L: -	2.4	0	no	no
8	T4a	N2c	Oropharynx HPV- Grade 2	R: II, III L: II, III	R: II, III L: II, III	−0.5	−0.6	no	no
9	T3	N1	Oropharynx HPV+ Grade 2	R: - L: II	R: - L: II	−2.4	<0.1	no	no
10	T3	N2c	Oropharynx HPV+ Grade 2	R: II, III L: II; III	R: II, III L: II; III	3.1	1.2	no	no
11	T2	N2b	Oropharynx HPV- Grade 3	R: II, III L: -	UFND	0.4	UFND	no	no
12	T4a	N2c	Oropharynx HPV- Grade 3	R: Ib, II, III L: III, IVa	R: Ib, II, III L: III, IVA	−2.5	−0.2	no	no
13	T4b	N2c	Hypopharynx Grade 3	R: II, VIb, VIIa L: -	UFND	25.5	UFND	no	no
14	T2	N2c	Oropharynx HPV- Grade 3	R: II L: II	UFND	0.6	UFND	no	no
15	T4a	N2b	Oral cavity Grade 2	R: II, VIIa L: -	R: II, VIIa L: -	−1.4	−0.2	no	no
16	T4a	N1	Oral cavity Grade X	R: - L: 1b	R: - L: 1b	−2.1	<0.1	no	no
17	T4a	N2b	Oral cavity Grade 2	R: Ib, II, III L: -	R: Ib, II, III, IVa, Vb L: -	2.2	18.2	+elective & high risk vol.	no
18	T4a	N2c	Oral cavity Grade 2	R: Ib, II, III L: Ib, II, III	R: Ib, II, III L: Ib, II, III	7.1	−2.6	+high risk vol.	no
19	T3	N2b	Oropharynx HPV- Grade 2	R: - L: II, III	R: - L: II, III	4.7	2.9	+high risk vol.	no
20	T2	N2b	Oral cavity Grade 2	R: II, III, IVa L: -	R: II, III, IVa L: -	0.6	−0.9	+high risk vol.	no
21	T4a	N2c	Oral cavity Grade 2	R: II, III, IVa L: Ib, II, III, IVa	R: II, III, IVa L: Ib, II, III, IVa	22.9	50.7	+high risk vol.	no
22	T4a	N2b	Oral cavity Grade 3	R: I, II, III L: -	R: I, II, III L: III, IVa	13.5	9.5	+elective & high risk vol.	yes
23	T3	N2b	Oral cavity Grade 3	R: II, III L: -	R: II, III L: -	1.5	0.6	+high risk vol.	no
24	T2	N2c	Oropharynx HPV- Grade 3	R: II L: III	R: II L: III, IVa	1.4	−4.3	+elective & high risk vol.	no
25	T4a	N2c	Oropharynx HPV+ Grade 3	R: Ib, II, III L: Ib, II, III	R: Ib, II, III L: Ib, II, III	116.5	2.3	+high risk vol.	no
26	T4a	N2c	Larynx Grade 3	R: II, III, IVa L: II, IVa	R: II, III, IVa L: II, III, IVa	−2.5	1.2	+high risk vol.	no
27	T4a	N2b	Oropharynx HPV- Grade 3	R: - L: II, III	R: - L: Ib, II, III	3.7	0.6	+high risk vol.	yes
28	T4a	N2c	Oropharynx HPV- Grade 2	R: Ib L: Ib, II, III, IVa	R: Ib, II, III, IVa L: Ib, II, III, IVa	1.1	2.7	+elective & high risk vol.	no
29	T2	N2b	Hypopharynx Grade 3	R: - L: II, III	R: - L: Ib, II, III	−0.2	1.3	+elective & high risk vol.	no
30	T4a	N0	Oropharynx HPV- Grade 2	R: - L: -	R: II, III L: II, III	2.3	3.4	+elective & high risk vol.	yes
31	T2	N1	Oropharynx HPV- Grade 3	R: III L: -	R: II, III, IVa L: -	5.3	8.4	+elective & high risk vol.	no
32	T2	N2c	Oropharynx HPV- Grade X	R: II L: II	R: II, III L: II, III, Va + b	7.9	0.4	+elective & +high risk vol.	no

MTV: metabolic tumor volume; L: left; R: right; UFND: upfront neck dissection; vol.: volume.
cT, cN and cM stages according to the Union for Cancer Control, 7th Edition.
* Would the new high-risk volume (defined by the second PET/CT) be covered by the initially planned elective volume?

from a second look PET/CT because of exponential tumor growth. In contrast, it is also possible that more upstaging would occur on the basis of a neck initially with no (cN0) or a lower (cN1–2a) burden of regional metastases. An upstaging in an already cN $\geq$ 2b case is less likely than a patient with cN0–2a because any newly emerging involved lymph nodes would upstage the disease in the latter case. Moreover, the clinical impact of upstaged early-stage HNSCC would be higher because a unimodal treatment concept would be switched to a multimodal

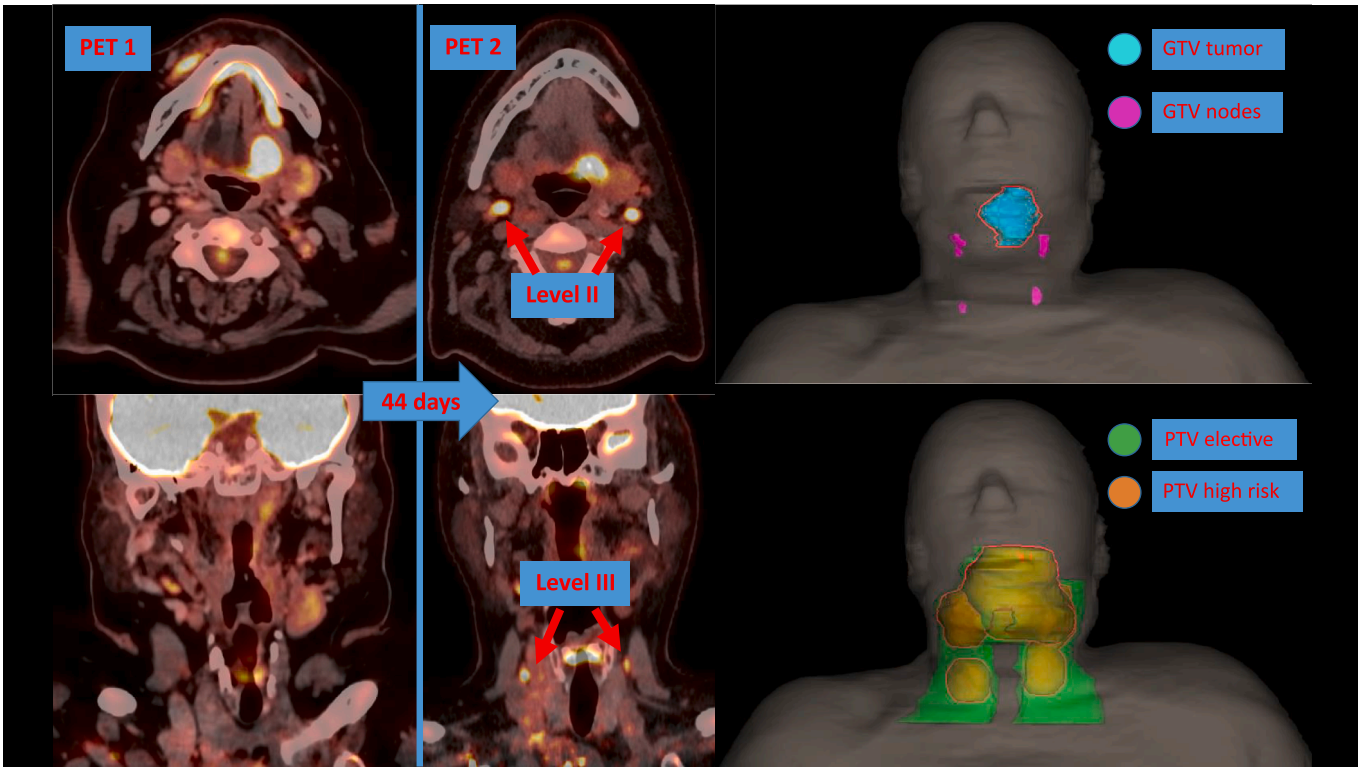

Fig. 2. Example case who was upstaged from cN0 to cN2c **Description of** Fig. 2**:** The second look PET/CT revealed two newly involved lymph nodes in Level II bilaterally and two in level III bilaterally. Based on this information, nodal high-risk volumes were added, and the elective volume was enlarged to include levels Va + b bilaterally. Please note the positioning discrepancy between two PET/CT scans because the first was diagnostic only, whereas the second was acquired in the treatment position.

strategy by treatment intensification, such as the addition of concomitant chemotherapy, altered fractionation or switch to primary surgery, corresponding to a major treatment change. Finally, yet importantly, the issue of cost effectiveness caused by repeated PET/CT is not trivial. In this context, the impact of an incorrect treatment indication (major treatment change) or an inadequate RT plan (minor treatment change) on tumor control and survival is substantial, and diagnosis by means of PET/CT was shown to be cost-effective in the long term [26–28]. Nevertheless, the potential long-term benefit of a second-look examination should be further investigated and validated. The question about the possible clinical advantage of repeated PET/CT in comparison with contrast-enhanced planning-CT only could be adequately addressed and answered in such a manner. Nevertheless, the current rates of locoregional control in comprehensive cancer centers would require a high number of patients in such cohorts to determine a statistically significant influence of the strategy demonstrated here.

Approximately 155 primary LAHNSCC cases are diagnosed annually and staged with PET/CT in our center. Although 32 patients within four years indicated good quality in terms of treatment delays, the sample size remained relatively small for the purposes of this study. Additional limitations of our study are due to its retrospective nature. Some clinical parameters, such as smoking and the exact reasons for the delay, could not be clearly defined. The time interval between the examinations was heterogeneous, although it did not seem to have a substantial impact or predictive value on the results. Moreover, it is possible that the rate of upstaging and treatment changes would be slightly different if four patients had not undergone upfront neck dissection.

Conclusion

A second look PET/CT due to a delay of more than four weeks to RT in LAHNSCC or in case of clinical suspicion of tumor progression led to tumor upstaging in 13% of patients and changes in treatment planning in more than half of patients, which is expected to directly influence oncologic outcome.

Declarations

Ethics approval and consent to participate: The study was approved by the regional ethics committee with project ID 2018–02009.

Consent for publication: All patients diagnosed in and after 2014 provided written consent for their data to be used for research and publication. Patients who were diagnosed prior to 2014 and declined to have their data used for research purposes (written or documented oral statement) were excluded from the study.

Availability of data and materials: Research data are stored in an institutional repository, and an anonymized version will be shared upon reasonable request to the corresponding author.

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CRediT authorship contribution statement

Olgun Elicin: Conceptualization, Methodology, Formal analysis, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing. **Bernd Vollnberg:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Mohamed Shelan:** Data curation, Writing - original draft, Writing - review & editing. **Elena Riggenbach:** Data curation, Writing - original draft, Writing - review & editing. **Beat Bojaxhiu:** Data curation, Writing - original draft, Writing - review & editing. **Etienne Mathier:** Data curation, Writing - original draft, Writing - review & editing.

Roland Giger: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Daniel M. Aebersold:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Bernd Klaeser:** Formal analysis, Project administration, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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