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Adherence to pretreatment and intratreatment imaging of head and neck squamous cell carcinoma patients undergoing (chemo) radiotherapy in a research setting

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ABSTRACT

Purpose: The emerge of improved personalized treatment adaptations and outcome prediction is accompanied with increasing non-invasive assessments in early treatment phase, leading to increased patient burden. This study assessed the adherence of patients with head and neck squamous cell carcinoma (HNSCC) to undergo pretreatment and research-related intratreatment imaging, and assessed which factors caused drop-out.

Method: Between 2013 and 2019, advanced-staged HNSCC patients were prospectively included, underwent (chemo) radiotherapy with curative intent and planned for both pre-treatment and intratreatment sequential 18F-FDG-PET/CT, 18F-FDG-PET/MRI and thereafter MRI (including DWI/DCE). Drop-out-factors were described as healthcare-related (logistics and imaging-system defects) and patient-related (psychological, physical, not-specified). Common Toxicity Criteria (CTC) were routinely scored by radiation/medical oncologists throughout the first 3 weeks, and compared between patient drop-outs and who complete imaging.

Results: Ninety-seven patients (mean age 61 ± 6.8 years) were included; 95 patients (97.9%) underwent pretreatment imaging and 63 (64.9%) intratreatment imaging. For 18F-FDG-PET/CT, 18F-FDG-PET/MRI and MRI pretreatment drop-outs were 2, 10 and 3 patients and for intratreatment drop-outs were 34, 39 and 35 patients, respectively. Patient-related drop-out-factors were physical (n = 16, e.g. dysphagia), psychological (n = 6, e.g. claustrophobia) and non-specified (n = 12). Healthcare-related drop-out-factors were logistics (n = 6) and 18F-FDG-PET/CT-/MRI-system defects (n = 2). The CTC mucosal toxicity was significantly higher (p = 0.023) at week 2 of (chemo)radiotherapy in patient drop-outs than with complete imaging.

Conclusions: The drop-out frequency of advanced-staged HNSCC patients for imaging during (chemo)radiotherapy in a research-setting was high and mainly patient-related. Treatment of patient-related inconveniences, communication of rationale and healthcare-related imaging protocol efficiency improvements may contribute to improved adherence.

1. Introduction

Throughout the past decades, treatment of head and neck squamous cell carcinoma (HNSCC) patients has been improved [1]. However, in advanced staged HNSCC patients recurrences generally occur in approximately 30% [2] and a mean 5-years overall survival of 50% is observed [3]. In order to provide the most optimal individual treatment for these patients, precision medicine targeting patient-specific characteristics of pretreatment clinical examination, histopathology and functional imaging is warranted [4]. Additionally, patient-specific tumoral response to (chemo)radiotherapy in early treatment phase might be assessed non-invasively by performing intratreatment functional imaging [5]. Consequently, based on early response assessment individualized treatment adaptations can potentially be made, such as de-

Abbreviations: CTC, revised common toxicity criteria; DCE, dynamic contrast-enhanced imaging; DWI, diffusion-weighted imaging; HNSCC, head and neck squamous cell carcinoma

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escalation [6], escalation [5] or change of treatment modality [7].

Optimization of treatment efficacy, when based on prognostic information of multiple time points [5], will easily result in more frequent imaging examinations [8]. Hereby, patient's compliance is essential, but logistical challenges and financial consequences accompanied with the implementation of extra examinations should be also taken into account [9]. Medical research may not be broadly generalizable to clinical practice due to patient's withdrawal from these imaging examinations, when they are performed too frequently or when the expected beneficence for the patient is not clear [10,11].

Patient adherence to prescribed medical interventions is an ever present and complex problem [12]. A patient's withdrawal from these additional imaging examinations could be due to latent factors or manifest factors. Latent factors, such as general discomfort, depression [13], anxiety [14] or a lack of motivation to comply, could have impact on the patients' own health outcomes, but these factors could also affect quality, relevance and implementation of imaging assessments [15]. An example of a manifest factor are physical constraints, such as radiotherapeutic and chemotherapeutic acute toxicity [16], which contributes to the patient's burden and might reduce patient willingness and ability to participate.

In order to improve precision medicine, it is important to explore the adherence of additional imaging examinations during treatment and to identify possible drop-out factors. This could bridge the gap between the increasing patient burden and the possibilities of improved treatment efficacy [4–7,17]. To our knowledge, previous studies on the adherence of additional imaging were mainly in a pretreatment screening setting [18–20] and a drop-out factor analysis of patients diagnosed with cancer complying for an additional imaging examination during treatment (intratreatment) has not been performed before. The aims of this study were to assess the adherence of HNSCC patients to undergo an additional imaging examination in a research setting, and to analyze the eventually associated drop-out.

2. Methods

2.1. Patient cohort

This prospective, single-center trial was approved by our ethics committee. The objective of this study protocol was to predict patients' outcome by performing functional imaging (^{18}F-FDG-PET/CT, ^{18}F-FDG-PET/MRI and MRI) of early tumor responses to (chemo)radiotherapy. Patients with previously untreated histologically proven advanced-staged (≥bulky T2 stage) HNSCC, planned for (chemo)radiotherapy (CRT) with curative intent were consecutively asked to participate In order to avoid heterogeneity patients < 18 years of age and pregnant were excluded as well as tumors at rare sites (i.e. sinonasal carcinomas), with different etiology (i.e. nasopharyngeal carcinomas) and too small to be clearly visible by imaging (i.e. < bulky T2 tumors), and treatments other than primary radiotherapy with or without chemotherapy (i.e. patients planned for surgical treatment). Within five weeks after baseline imaging, (chemo)radiotherapy was initiated. Treatment consisted of a pre-determined regimen of 70 Gy radiotherapy in 35 fractions during a period of seven weeks, with or without concomitant chemotherapy; consisting of 3-weekly a cisplatin (100 mg/m^2) or weekly cisplatin (40 mg/m^2). Written informed consent was obtained from all patients by a dedicated researcher. Patients that dropped-out of the imaging protocol, received the same treatment as patients who completed all imaging successfully. The method of communication was a treatment-independent conversation between a dedicated researcher with the patient, subsequent to the conversation between the otolaryngologist, radiation oncologist and the patient, who were independent from the study. HPV-status was determined by p16 immunostaining followed by HPV DNA-PCR on the p16-immuno-positive cases [21]. The overall alcohol and nicotine use was registered.

2.2. Imaging work-flow

Patients underwent pretreatment and intratreatment (on day 10 of (chemo)radiotherapy) imaging, consisting of sequential acquisition of first an ^{18}F-FDG-PET/CT, secondly an ^{18}F-FDG-PET/MRI and thirdly a MRI with DWI- and DCE-MRI acquisition (Fig. 1), which were performed on the same day.

^{18}F-FDG-PET/CT was performed according the EANM guidelines 2.0 on a Gemini TF PET/CT (Philips Healthcare) with EARL accreditation [22]. Patients fasted for 6 h and at 60 min after intravenous administration of ^{18}F-FDG, a dedicated Head-Neck PET/CT-scan was performed in arms-down-position in a radiotherapeutic radiation mask, from-lung-apex-to-skull-vertex with 4 min per bed-position. Thereafter, only pretreatment a whole-body ^{18}F-FDG-PET/CT (2 min per bed-position) was performed without mask, in arms-up-position from-mid-thigh-to-skull-vertex. The total time of pretreatment dedicated head-and-neck ^{18}F-FDG-PET, diagnostic CT and whole body ^{18}F-FDG-PET/CT was 30 min. The total acquisition time of the intratreatment ^{18}F-FDG-PET and low-dose CT examination, without a whole body ^{18}F-FDG-PET/CT was 15 min.

Subsequently, patients were directly (40 min interval) transported to the 3.0 T Ingenuity PET/MRI-system (Philips Healthcare) performing a ^{18}F-FDG-PET at 140 min post-injection of the lungs to apex of the skull. The total acquisition time of the ^{18}F-FDG-PET on the PET/MRI-system was 15 min.

Directly thereafter, an MRI was performed utilizing a 16-channel neurovascular coil on the MRI of the PET/MRI system. Conventional sequences of axial T1-weighted (T1w), T1w-post-gadolinium, T2-weighted (T2w) and short T1 inversion recovery (STIR), DWI was acquired using a single-shot spin-echo echo-planar imaging (SS-SE-EPI). DCE-MRI was performed with intravenous injection of 0.2 mmol/kg bodyweight Gd-DOTA (Dotarem). The total MRI acquisition time was 45 min.

2.3. Drop-out classification

Adherence was defined as the willingness, ability and possibility to participate in the imaging acquisition protocol. A drop-out was defined as a patient, who waived adherence before or during the imaging acquisition or when acquisition failed due to any circumstance. The adherence at the pre-treatment and intratreatment acquisition of all modalities were assessed as well as the adherence per modality. The possible patient drop-out factors were evaluated with the patient after inclusion in the study and before, during and after imaging acquisition, by collecting all motivations for withdrawal or factors, which were responsible of drop-out. Pretreatment drop-outs automatically dropped out for the intratreatment phase.

The drop-out factors to undergo imaging were divided into 2 categories; I) patient-related and ii) healthcare-related. The patient-related factors were divided in A. psychological, B. physical and C. non-specified factors. Psychological claustrophobia was defined as the non-adherence or discontinuation of the imaging acquisition due to known or new manifestation of anxiety of confined places. The healthcare-related factors were divided in A. logistic factors and B. imaging-system defects.

The revised common toxicity criteria (CTC) version 2.0 [23], was prospectively weekly performed basis by the radiation oncologist and extracted from patient records in order to assess the toxicity level throughout the first 3 weeks of treatment in order to capture differences and/or trends. In order to gain insight in the adherence and drop-out factors over time, the number of patients with complete imaging and patients drop-outs of pretreatment and intratreatment imaging was assessed per year.

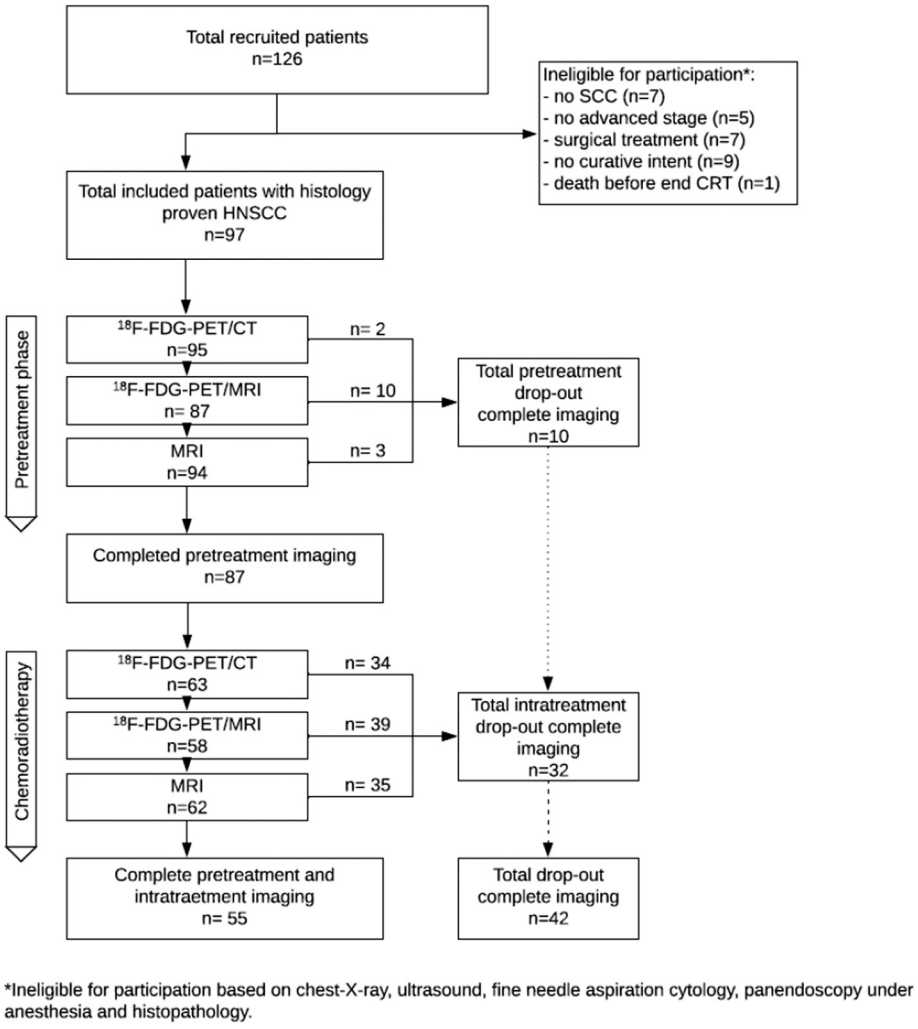

Fig. 1. Flowchart of patient adherence.

2.4. Statistical analysis

The differences between patients with complete imaging and patients who dropped out was assessed with the Mann-Whitney *U* test. The mean CTC-scores were compared between the both patients groups for week 1, 2 and 3 during treatment, performing the Mann-Whitney U test. In order to compare the outcome (recurrence-free, metastasis-free and overall survival) of both patient groups the log-rank test was performed ($p < 0.05$ was considered statistically significant). Analyses were performed using SPSS (version 18.0; SPSS Inc.).

3. Results

3.1. Patients characteristics

From August 2013 to January 2019, 126 consecutive patients were prospectively recruited in the diagnostic workup phase. Twenty-nine patients were excluded, of which 7 patients with a non-squamous cell carcinogenic histology, 7 patients underwent surgical treatment, 9 patients underwent non-curative treatment, 5 patients were diagnosed with a non-bulky T2-staged HNSCC and one patient died during treatment (not tabulated).

The final study population consisted of 97 patients, with a mean age of 60 years (interquartile range (IQR) 55–67) and consisted of 70.1% male patients (Table 1). Primary tumors were located in the oropharynx (n = 74), hypopharynx (n = 13) and larynx (n = 10). In 32 of the 74 patients (43.2%) with oropharyngeal cancer the HPV-status was positive. The median follow-up time of the total study population was 20.6 months (IQR 14.3–36 months) with 22 recurrences, 20 metastases and 26 deaths.

3.2. Adherence analysis

Ninety-seven patients (100%) were included in total. The pretreatment group consisted of 78 patients (89.7%), including 68 males (70.1%), underwent complete pretreatment imaging. The intratreatment group consisted of 58 patients (59.8%), including 48 males (49.5%), underwent complete intratreatment imaging. The complete imaging group consisted of 55 patients (56.7%), underwent complete pretreatment and intratreatment imaging (complete imaging group) (Fig. 1). The drop-out group consisted of 42 patients, who dropped-out at pretreatment or intratreatment imaging.

In the pretreatment group, 95 (97.9%), 87 (89.7%) and 94 patients (96.9%) underwent ^{18}F-FDG-PET/CT, ^{18}F-FDG-PET/MRI and MR-imaging and in the intra-treatment phase 63 (64.9%), 58 (59.8%) and 62 patients (63.9%), respectively. The total number of dropped-out patients was 42 (43.3%); of whom 2, 10 and 3 patients, respectively dropped-out at pretreatment imaging, and 34, 39 and 35 patients dropped-out during treatment ^{18}F-FDG-PET/CT, ^{18}F-FDG-PET/MRI and MR-imaging, respectively.

The median follow-up time of the complete imaging group (n = 55) was 14.2 months (IQR 6.3–24.9) with 11 recurrences, 11 metastases

Table 1
Baseline characteristics.

Patient characteristics	Total	Pretreatment			Intratreatment		
Total included patients (n, %)	97 (100%)						
Age, y (IQR)	60 (55–67)	60 (55–67)			61 (55–66.5)		
Male patients (n, %)	68 (70.1%)	68 (70.1%)			48 (49.5%)		
T-stage (n, %)							
2	32 (33%)	32 (33%)			21 (65.6%)		
3	24 (24.7%)	24 (24.7%)			19 (79.2%)		
4	41 (42.3%)	41 (42.3%)			25 (61%)		
N-stage (n, %)							
0	20 (20.6%)	20 (20.6%)			15 (15.5%)		
1	20 (20.6%)	20 (20.6%)			11 (11.3%)		
2	54 (55.7%)	54 (55.7%)			35 (36.1%)		
3	3 (3.1%)	3 (3.1%)			2 (2.1%)		
Location primary tumor (n, %)							
Oropharynx	74 (76.3%)	74 (76.3%)			54 (55.7%)		
Hypopharynx/larynx	23 (23.7%)	23 (23.7%)			13 (13.4%)		
Positive HPV-status oropharynx (n, %)	32 (43.2%)	32 (43.2%)			21 (38.9%)		
Daily alcohol (unit per day, range)	2 (0.5–4.38)	2 (0.5–4.38)			2 (0.5–4.75)		
Smoking (pack years, range)	30 (11–43.2)	30 (11–43.22)			29.5 (0.63–43.07)		
Imaging	Total patients	^{18}F-FDG-PET/CT	^{18}F-FDG-PET/MRI	MRI	^{18}F-FDG-PET/CT	^{18}F-FDG-PET/MRI	MRI
Complete pre- and intratreatment imaging	97 (100%)	55 (56.7%)					
Complete imaging per imaging-phase	97 (100%)	87 (89.7%)			58 (59.8%)		
Complete imaging per modality	97 (100%)	95 (97.9%)	87 (89.7%)	94 (96.9%)	63 (64.9%)	58 (59.8%)	62 (63.9%)
Total patient drop-outs per modality	42 (43.3%)	2 (2.1%)	10 (10.3%)	3 (3.1%)	34 (35.1%)	39 (40.2%)	35 (36.1%)
Patient-related drop-out	34 (35.1%)	1	7	2	28	32	30
A. Psychological	6	0	2	1	5	6	5
B. Physical	16	0	3	1	13	15	16
C. Not-specified	12	1	2	0	10	11	9
Healthcare-related drop-out	8 (8.2%)	1	3	1	6	7	5
A. Logistics	6	1	2	1	5	6	5
B. Imaging system defect	2	0	1	0	1	1	0

The baseline characteristics of the 97 included patients. Furthermore, an overview of the adherence of patients at the imaging acquisitions is shown. The total patient drop-outs per modality shows that the intratreatment dropouts were higher than the pretreatment dropouts. Finally, the number of patient-related (category A–C) and healthcare-related (A, B) dropouts were shown.

and 13 deaths occurring, whereas the median follow-up in the drop-out group (n = 42) was 17.7 months (IQR 6.6–32.3) with 11 recurrences, 9 metastases and 13 deaths.

3.3. Drop-out factor analysis

The overall pretreatment and intratreatment patient-related drop-out was 34 patients (35.1%) of the total 42 dropouts (43.3%) (Table 1);

A. Psychological factors caused 6 drop-outs, who were affected by claustrophobia for the imaging system or the radiation mask.
B. Physical factors caused 16 drop-outs, of whom 8 patients were affected by dysphagia (n = 8 patients) causing a choking sensation and difficulty to swallow the increased mucus production during imaging. Furthermore, other physical factors were nausea due to chemotherapy (2 patients), acute kidney injury due to cisplatin (2 patients). Four patients were unable to complete the imaging protocol; due to the inability to lie down for a long time due to arthrosis, obesity or due to a vasovagal collapse (4 patients).
C. Non-specified factors caused 12 drop-outs, who could not formulate a concrete reason to drop out. However these patients mentioned an idea of noxiousness of the imaging techniques and the loudness of the MRI.

The overall pretreatment and intratreatment healthcare-related factors caused drop-out in 8 patients (8.2%) of the total 42 dropouts (Table 1);

A. Six dropped-out due to logistic issues (e.g. incorrect scheduling of patients, protocol deviation).
B. Two patients dropped-out due to an imaging system defect.

3.4. Adherence over time

Throughout the years of patient inclusion, the amount of successfully completed pre- and intratreatment imaging increased along with the total imaging examinations (Fig. 2A). The percentage of drop-outs per year at pretreatment imaging phase decreased over time (100% to 36%), of which there was only one inclusion in the first year. The percentage of drop-outs at intratreatment imaging phase also decreased over time (60% to 0%) (Fig. 2B). The intratreatment drop-out factor distribution (Fig. 2C) consisted over time mainly of physical and not-specified factors.

3.5. Comparison of patient groups

No significant differences were found for clinical parameters or patient's outcome between complete imaging patients and drop-outs (Table 2). The acute mucosal toxicity was found significantly higher in drop-outs than in patients undergoing complete imaging (p = 0.023; Table 3, Supplement 1).

The patient- and healthcare-related factors could be divided in occult (i.e. non-specified factors) and overt factors (e.g. claustrophobia, imaging-system maintenance), which were addressed by the investigators in order to prevent drop-outs and to formulate recommendations per drop-out factor (Table 4). The analysis of recurrence-free, metastasis-free and overall survival did not result in significant difference between patient drop-outs compared with patients who underwent complete imaging (p = 0.514, p = 0.647, p = 0.826, respectively).

4. Discussion

In this study, the patients' adherence and drop-outs of HNSCC

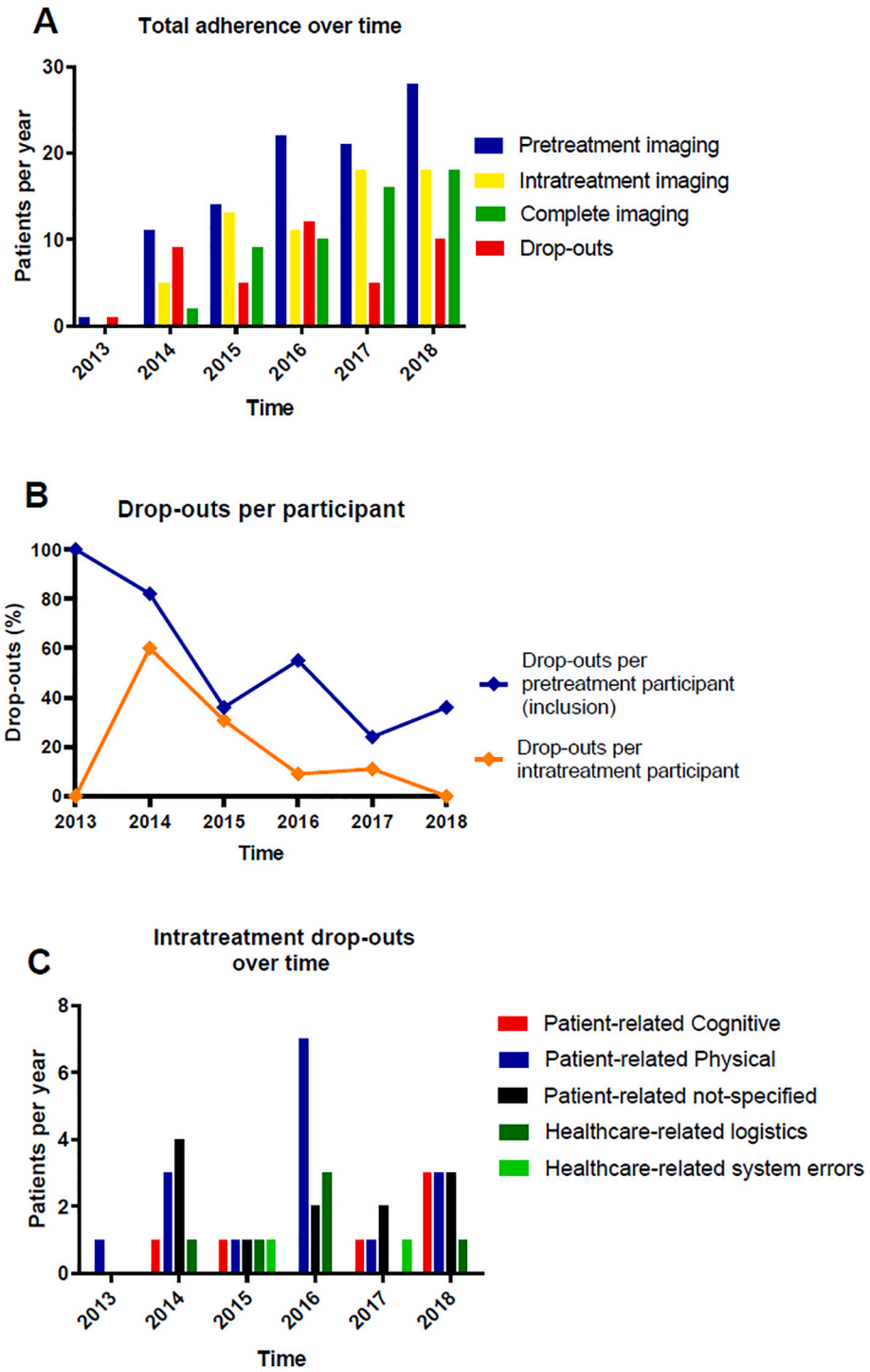

Fig. 2. Adherence over time.
A) The total adherence per year of pretreatment (blue) and intratreatment (yellow) patients and those who underwent complete imaging (green) and those who dropped-out (red). B) The percentage of drop-outs per year corrected for the amount of included patients (blue; pretreatment patients) and the percentage of drop-outs per participant at the intra-treatment imaging (orange). C) The different patient- and healthcare-related drop-out factors of patients over time. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patient to undergo pretreatment and intratreatment imaging were assessed. Several patient-related and healthcare-related drop-out factors were identified, which allowed for a specific drop-out factor approach. This may have led to a decrease in drop-out percentage per participant over time, although the amount of inclusions and intratreatment participants increased.

4.1. Patient-related drop-out

The patient drop-out at pretreatment imaging was low. Main drop-out factors were psychological anxiety, physical inability to complete the long duration of the imaging protocol and non-specified factors. At intratreatment imaging a high dropout was found at all modalities, which was mainly caused by physical or non-specified factors.

Table 2
Parameter differences between patients with complete and patient-related drop-out.

Total = 97 included patients		Complete imaging N = 55	Patient-related drop-out N = 42		Drop-out per patient-related category		
		Total	Total	p-Value*	Psychological	Physical	Not-specified
Total	Patient outcome						
	Recurrences (%)	11 (20%)	11 (26.2%)	0.51	2 (4.8%)	0	8 (19.0%)
	Metastases	11 (20%)	9 (21.4%)	0.65	2 (4.8%)	1 (2.4%)	6 (14.3%)
	Deaths	13 (23.6%)	13 (30.9%)	0.83	2 (4,8%)	2 (4.7%)	7 (16.7%)
Pretreatment	Number of patients	55	8	p-Value**	2	4	2
	Age (median, SD)	61 (8.3)	62.5 (6.1)	0.34	63 (2.8)	65.5 (4.4)	61 (4.4)
	Gender	1 (0.5)	1 (0.4)	0.39	1 (0)	1 (0.4)	1 (0.6)
	T-stage	3 (0.9)	3 (0.7)	0.69	3 (1)	3 (0.5)	3 (0.5)
	N-stage	2 (0.9)	2 (0.9)	0.99	1 (1)	2 (0.5)	2 (0.9)
	HPV-status	0 (0.5)	0 (0.3)	0.21	0.5 (0.5)	0 (0)	0 (0)
	Alcohol use	2 (1.4)	1.5 (0.7)	0.59	1.5 (0.5)	1 (0.8)	2 (0.5)
	Daily alcohol use	2 (4.6)	2.3 (2.1)	0.88	2.6 (2.4)	5 (2.4)	2 (0.8)
	Smoking PY	25 (18.8)	35 (16.2)	0.38	21 (9)	45 (10.8)	40 (19.4)
	Smoking years stopped	0 (0.5)	1.5 (4.1)	0.27	10 (1)	0 (1.4)	0 (1.9)
During treatment	Number of patients	55	34	p-Value**	6	16	12
	Age (median, SD)	62 (8.3)	61 (7.5)	0.50	63 (10.4)	62.5 (6.3)	58 (6.7)
	Gender	1 (0.5)	1 (0.4)	0.93	1 (0.4)	1 (0.4)	1 (0.5)
	T-stage	3 (0.9)	3.5 (0.9)	0.69	3 (0.9)	4 (0.7)	3 (0.9)
	N-stage	2 (0.9)	2 (0.8)	0.83	2 (0.8)	2 (0.6)	2 (0.8)
	HPV-status	0 (0.5)	0 (0.5)	0.21	0 (0.5)	0 (0.4)	0 (0.5)
	Alcohol use	2 (1.4)	1.5 (1.2)	0.84	2 (1.3)	1.5 (1.2)	2 (1.3)
	Daily alcohol use	2 (4.7)	2 (3.3)	0.60	2 (3.4)	2.25 (3.3)	2 (3.4)
	Smoking PY	25 (18.8)	32.5 (16.3)	0.48	25 (17.3)	35 (14.6)	25 (17.3)
	Smoking years stopped	0 (0.5)	0 (7.4)	0.20	0 (5.8)	0 (8.7)	0 (5.8)

Differences of clinical parameters between patients with complete imaging and drop-outs.
On the right, the clinical parameters were shown of patients who were stratified per drop-out category.
* Patient outcome assessed using the Log-rank test (significance threshold $p < 0.05$).
** Clinical parameters of the pretreatment and intratreatment patients assessed using the Mann-Whitney U test (significance threshold $p < 0.05$).

The physical burden was the most common cause of intratreatment drop-out, consisting of radiation side-effects and dysphagia, which might be due to the volume of the advanced staged tumor and obstructive location through which saliva accumulation occurs. Another drop-out factor was nausea, caused by chemotherapy, which might be redressed if it is identified on time. This early identification and addressment of treatment inconveniences could have been an important factor of improved adherence over time. Newell et al. [24] stated that the accuracy of perception of reported physical and psychosocial experiences by the patient could be improved. Some predictive physical constraints could be captured by assessing the variations in the acute toxicity throughout treatment and resolved by addressing them once noticed. In this study the mucosa toxicity in the second week of treatment was significant higher in the drop-out patients compared with those who underwent complete imaging. A possible explanation of drop-out was the discomfort of mucosal toxicity (i.e. erythema and pain) due to (chemo)radiotherapy. Although studies reported on early toxicity due to (chemo)radiotherapy, such as confluent mucositis, dysphagia, pain on swallowing [25–28], none of them assessed the predictive value of early treatment toxicity to predict the patient willingness or ability of adherence to intratreatment imaging.

Non-specified arguments might have been present occultly, which caused resistance of patients and which could have been difficult to identify in order to address them efficiently. Patients were asked to comply for the extended pretreatment imaging and the intratreatment imaging as part of a scientific research without clear direct benefit for the patient's treatment or outcome. This might have resulted in lower adherence. Patients tend to adhere more to the standard of care examination. Therefore, communication of the rationale of the research imaging is critical to improve the adherence rate in future studies. Furthermore, we found that a bothersome pre-treatment imaging experience such as a system error or increased scan-time could be redressed by robust preparation. Finally, the presence of patient doubt about the noxiousness of imaging should be handled in the pretreatment phase already, which could be done by an extensive explanation of the techniques.

The main psychological burden causing intratreatment drop-out was anxiety. Although the first experience at pretreatment imaging did

Table 3
Common toxicity score over time

	Week 1			Week 2			Week 3		
N = 89 patients	Complete	Drop-out	p-Value	Complete	Drop-out	p-Value	Complete	Drop-out	p-Value
Acute toxicity									
Skin	0.054 ± 0.23	0.15 ± 0.36	0.148	0.18 ± 0.39	0.29 ± 0.52	0.349	0.82 ± 0.43	0.65 ± 0.49	0.101
Mucosa	0.073 ± 0.26	0.18 ± 0.39	0.143	0.45 ± 0.63	0.91 ± 0.87	**0.023**	1.47 ± 0.90	1.47 ± 0.96	0.993
Xerostomia	0.2 ± 0.4	0.24 ± 0.43	0.727	0.58 ± 0.6	0.53 ± 0.56	0.663	1.02 ± 0.59	0.88 ± 0.69	0.318
Pharynx	0.35 ± 0.55	0.56 ± 0.93	0.533	0.69 ± 0.79	0.94 ± 0.89	0.176	1.29 ± 0.96	1.32 ± 1.04	0.952
Larynx	0.2 ± 0.65	0.21 ± 0.77	0.597	0.33 ± 0.88	0.38 ± 0.85	0.486	0.35 ± 0.78	0.41 ± 1.05	0.715
Medication	1.07 ± 1.32	0.85 ± 1.28	0.337	1.2 ± 1.32	1.41 ± 1.44	0.485	1.85 ± 1.25	1.91 ± 1.31	0.804

The mean revised common toxicity criteria [23] (scored by radiotherapists) throughout week 1, 2 and 3, were stratified in 2 groups; patients with complete imaging and drop-outs. The toxicity differences between the 2 patient groups was assessed with the Mann-Whitney U test.

Table 4
Dropout factors and recommendations.

Patient-related			Healthcare-related		
Latent	Manifest	Recommendations		Manifest	Recommendations
Psychological	Claustrophobia	- Prescribe anxiolytic medication - Comfort the patient by explaining the patient about using the emergency button and exiting the scanner procedure. - Communicate during the scan with the patient - Install a mirror on the neuro-vascular coil to look outside the scanner	Logistics	^{18}F-FDG-PET uptake interval expansion	- Align interdisciplinary tasks of healthcare practitioners. - Reserve more time for immobile or old patients to get ready
	Noise MRI	- Put earplugs deep into the ears, combined with an ear protecting aid.		NV-coil removal forgotten at the PET-MRI imaging	- Remind different scanning steps - Remind the patient to lie still during the removal of the NV-coil
Physical	Nausea	- Prescribe anti-emetics or benzodiazepines - Prevent eating before scan		Placement of shimboxes with different sizes (part of tumor not in FOV)	- Perform a check by an radiologist or assistant.
	Dysphagia	- Instructions to swallow only between two imaging sequences.		Planning maintenance	- Take maintenance appointments of imaging manufacturers into account
	Unable to lie flat (e.g. arthrosis)	- Optimize pain management - Position a pillow behind the back to position the patient in the coil.	System errors	Errors PET/MRI during imaging	- Test imaging protocol before patient arrival
	Kidney insufficiency	- Patient admission in the hospital to provide an intravenous pre-hydration, allowing for contrast-enhanced CT and MRI.			
	Obesity or voluminous neck	- Assess size of the neck and the neuro-vascular imaging coil. - Assess weight and the allowed maximum weight of the imaging table.			
	Movement head, neck, tongue, swallowing	- Instructions before each sequence not to turn, swallow, talk, or move the tongue, head or neck during the noise of the imaging.			
Not-specified	Fright of noxiousness of imaging techniques	- Mention the low radiation dose of the ^{18}F-FDG-PET scan and CT-scan.			
	Length of scan	- Agree upon most important sequences - Reduce amount of bed-positions of the PET-scan			

The patient-related and healthcare-related drop-out factors with the suggested recommendations.

not cause high dropouts, the intratreatment drop-out were mainly caused by claustrophobia in the MRI. A suggestion for early identifying claustrophobia is to perform a dummy scan or try-out [29], in order to get used to the acquisition experience or to estimate the extent to which imaging is likely to succeed with or without anxiolytic medication. Anxiety for imaging examination was only mentioned previously in screening studies [18–20]. However in these studies anxiety was mainly to be diagnosed with cancer. However, in this study patients were aware of their cancer diagnosis. Previously described recommendations, such as psychosocial support and education to explore the patient's need [14,29] were increasingly implemented throughout the progress of this study. An extensive explanation of the imaging process and patient contact during the scan, were in this study most useful. Over time, this resulted in a decrease of drop-out percentage per included patient.

4.2. Healthcare-related drop-out

Current study comprised complex time-dependent image acquisitions, which could have made the research protocol more prone to protocol failures and possibly increased the non-specified patient burden. Improvements of time/logistics and imaging protocol duration should be made. Optimization of image quality was described previously [30]. However, optimizing efficiency and applicability of (intratreatment) imaging might be achieved by standardized planning of smaller imaging stacks due to knowledge of pretreatment imaging, reducing the amount of b-values at diffusion-weighted MR-acquisition and leave out less predictive modalities.

4.3. Applicability

The acquisition of intratreatment imaging allows for the assessment of tumoral changes due to treatment, which might offer opportunities to optimize patient-specific treatment adaptations in an early stage after treatment initiation [5,31]. The success of these necessary 'extra' intratreatment imaging assessments is dependent on patient adherence. In this study the adherence was not significant different between good and adverse patient outcome, suggesting no prognostic interference of drop-out factors. Furthermore, adherence increased over time, whereas the amount of drop-outs decreased, which might be caused by earlier identification of drop-out factors, solving of health-care related issues and dealing with patient-related psychological, physical of non-specified factors. A positive spiral with a reduction of extensive imaging protocol, could consequently increase willingness and ability to participate, which results in more evidence-based data, which leads to more benefits for the patient (i.e. accurate personalized outcome predictions and possible treatment optimisations) and consequently a higher adherence.

4.4. Limitations

In this study selection bias might have occurred by the inclusion of patients undergoing non-research-related (pretreatment) diagnostic imaging, which was important for treatment planning, extended with the research-related intratreatment imaging, of which adherence was only possible when they participated in pretreatment imaging. The lack of evidence-based benefits of the intratreatment imaging for the patient might have led to higher (non-specified) drop-outs.

Secondly, the sequential imaging acquisition setup of ^{18}F-FDG-PET/CT and ^{18}F-FDG-PET/MRI followed by an extensive MRI protocol, and it had to be done in correct order and in a limited timeframe, which might have been too heavy for weakened patients. For example, the ^{18}F-FDG-PET had to be done at exact time points, and a ^{18}F-FDG-PET/MRI could not been performed when there was no ^{18}F-FDG-PET tracer injection at the ^{18}F-FDG-PET/CT, which resulted in a higher drop-out at the ^{18}F-FDG-PET/MRI acquisition. Also, if a patient dropped out at the pretreatment imaging, automatically the patient was withdrawn from the intratreatment phase. In the current prospective study no pre-selection of fit patients was performed, however early identification and treatment of possible drop-out factors by clinicians (Table 4), may have caused the decreased drop-out rate. A dedicated researcher assisted the (independent) clinicians in identifying drop-out factors, who both might have been subject to an improving learning curve. Also, bias due to researcher-related dropout differences might have occurred. This however, could not be assessed in this study and should be evaluated in future studies with multiple researchers. The adherence of patients might be further optimized with a shortened and more efficient imaging protocol, but remains to be elucidated.

5. Conclusions

The drop-out factors of advanced stage head and neck squamous cell carcinoma patients in sequential pretreatment and intratreatment PET/CT and PET/MRI imaging during (chemo)radiotherapy were mainly patient-related (e.g. treatment induced inconveniences). Treatment of patient-related inconveniences, communication of the rationale and healthcare-related imaging protocol efficiency improvements may contribute to a higher patient adherence.

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