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Research manuscript

Use of 18F-FDG PET/CT Imaging for Radiotherapy Target Volume Delineation after Induction Chemotherapy and for Prognosis of Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-SCCHN)

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Abstract: *Background and objectives:* Induction chemotherapy (ICT) before definitive chemoradiation (CRT) gives high response rates in LA-SCCHN. However, pre-ICT gross tumour volume (GTV) for radiotherapy (RT) planning is still recommended. As ^{18}F-FDG PET/CT has an advantage of biological tumour information comparing to standard imaging methods, we aimed to evaluate the feasibility of ^{18}F-FDG PET/CT-based post-ICT GTV delineation for RT planning in LA-SCCHN and to assess the prognostic value of PET parameters: maximum standardized uptake value (SUV_{max}), metabolic tumour volume (MTV) and total lesion glycolysis (TLG). *Methods:* 47 LA-SCCHN patients were treated with 3 cycles of ICT (docetaxel, cisplatin, and 5-fluorouracil) followed by CRT (70 Gy in 35 fractions with weekly cisplatin). Pre- and post-ICT PET/CT examinations were acquired. Planning CT was co-registered with post-ICT PET/CT and RT target volumes were contoured according to post-ICT PET. Post-ICT percentage decrease of SUV_{max}, MTV and TLG in primary tumour and metastatic regional lymphnodes (LN) was counted. Loco-regional failure patterns, 3-year progression free (PFS) and overall survival (OS) were evaluated. *Results:* 3-year PFS and OS rates for study population were 67% and 61% respectively. 31.9% of patients progressed loco-regionally. All progresses were localised in high-to-intermediate dose (60 - 70Gy) RT volumes and none in low dose (50 Gy) volumes. Decrease of SUV_{max} ≥74% (p = 0.03), MTV ≥68% (p = 0.04), TLG ≥76% (p = 0.02) in primary tumour, and LN TLG decrease ≥74% (p = 0.03) were associated with PFS. Decrease of primary tumour SUV_{max} ≥74% (p = 0.04), MTV ≥69% (p = 0.04), TLG ≥74% (p = 0.02) and LN TLG ≥73% (p = 0.02) were prognostic factors for OS. *Conclusions:* According to our results, ^{18}F-FDG PET/CT-based post-ICT GTV delineation is feasible strategy without negative impact on loco-regional control and survival. Percentage decrease of metabolic PET parameters SUV_{max}, MTV and TLG has a prognostic value in LA-SCCHN.

Keywords: head and neck cancer; induction chemotherapy; ^{18}F-FDG PET/CT; target volume delineation

1. Introduction

Despite the absence of definitive scientific evidence, induction chemotherapy (ICT) for locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) is often used in clinical practice [1]. Up to 80 - 90% of patients with LA-SCCHN respond to cisplatin-based ICT and 20 - 40% of them achieve complete response (CR) [2]. Although several studies reported no benefit of ICT in terms of survival [2-4], it has a role in selected cases if there is likely to be a delay between diagnosis and starting definitive chemoradiotherapy (CRT) and in organ preservation strategies [5]. The current guidelines suggest that pre-ICT primary site and nodal gross tumour volumes (GTV) should be used for radiotherapy (RT) planning in cases when ICT is given [6-8]. However, possible superiority of post-ICT over pre-ICT GTV is now under investigation [9,10]. The potential advantages of using post-ICT imaging for target volume delineation include reduction of GTV due to tumour shrinkage and possibility to spare normal tissues. However, it bears a potential risk of missing partial tumour volume and, in some cases, difficulties in GTV delineation due to metabolic switch [9,11]. Contrast-enhanced computed tomography and/or magnetic resonance imaging are the standard methods for evaluating tumour response to ICT, and are mostly used for GTV delineation in LA-SCCHN. Recent studies report an emerging role of positron emission tomography (PET) with ^{18}Fluorine-labeled 2-fluoro-2-deoxyglucose integrated with computed tomography (^{18}F-FDG PET/CT) in RT planning for head and neck cancers due to the added biological tumour information. However, there is a lack of knowledge weather the use of ^{18}F-FDG PET/CT based post-ICT GTV delineation in RT planning is a feasible approach. Furthermore, earlier clinical studies demonstrated, that some parameters of ^{18}F-FDG PET/CT may predict the tumour chemosensitivity and LA-SCCHN patient survival [12-14]. Such ^{18}F-FDG PET/CT parameters as maximum standard uptake value (SUV_{max}), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) have been shown to correlate with LA-SCCHN patient outcome [15-17]. However, the prognostic value of the percentage decrease of these FDG uptake parameters from baseline to post-ICT is unknown.

The aims of our prospective phase II study were:

1. To evaluate the feasibility of ^{18}F-FDG PET/CT-based post-ICT GTV delineation strategy for LA-SCCHN RT planning by analysing patterns of local and/or nodal disease failure after CRT and assessing progression free survival (PFS) overall survival (OS) and treatment safety;
2. To assess the correlation of post-ICT percentage decrease of three metabolic^{18}F-FDG PET/CT parameters SUV_{max}, MTV and TLG in primary tumour and metastatic nodes with radiological response to ICT, PFS and OS.

2. Material and methods

2.1 Study design and patient selection

Between September 2013 and January 2016, patients affected by LA-SCCHN were enrolled in this phase 2 prospective cohort study. All subjects signed the informed consent form. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Lithuanian Bioethics Committee (No. BE-2-51) and was registered at www.clinicaltrials.gov (identification no. NCT02047201). All patients have been validated by the multidisciplinary team for ICT followed by CRT. The eligibility criteria were as follows: histologically confirmed locally advanced (stage III and IV) head and neck squamous cell carcinoma, Eastern Cooperative Oncology Group performance status (ECOG) 0 or 1, signed written informed consent. Patients with a known history of another cancer or suspected metastatic lesions were excluded.

2.2 ICT delivery and evaluation of response to ICT

Patients received three cycles of docetaxel, cisplatin, and 5-FU (TPF) ICT consisting of docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) administered as a 1-hour infusion on a day 1 and 5-fluorouracil (5-FU) (750 mg/m^2) administered by continuous infusion on days 1–5 [18]. Cycles were administered every 3-weeks. The reductions of the docetaxel, cisplatin and 5-FU doses were planned depending on the individual treatment tolerance and toxicity.

According to post-ICT ^{18}F-FDG PET, patients were classified into: ICT-responders – patients with ≥50% hypermetabolic tumour volume reduction, and ICT-non-responders – <50% reduction.

2.3 ^{18}F-FDG PET/CT examination and GTV delineation

Two ^{18}F-FDG PET/CT examinations were performed for each patient. The first one was whole-body ^{18}F-FDGPET/CT prior ICT during initial staging, another one 14±2 days after the last cycle of ICT including only head and neck region for therapeutic evaluation and CRT planning [7,11,13]. Post-ICT scan was acquired in intensity modulated radiation therapy (IMRT) treatment position with the five-point fixation thermoplastic mask. All ^{18}F-FDGPET/CT studies were performed on GE Discovery XCT (General Electric Healthcare system, United States of America) scanner. All PET/CT images were reconstructed with the ordered subset expectation maximization (OSEM) iterative algorithm using scatter correction with the 5 mm Gaussian filter on 128 x 128 and 256 x 256 matrixes. All acquired data was transferred to radiotherapy treatment planning system Eclipse (version v8.6) and registered by aligning the centres of the datasets. Planning CT was rigidly co-registered with post-ICT ^{18}F-FDGPET/CT for delineation of treatment volumes. The gross tumour volume GTV70 and gross nodal volume GTV60 were manually contoured using a visual interpretation technique on post-ICT PET images by radiation oncologist in collaboration with an experienced nuclear medicine physician. Clinical target volumes (CTV) of primary tumour CTV70 obtained by adding 5 mm margin to GTV70. CTV60 involved GTV70 and GTV60 plus 5mm margin. The elective CTV (CTV50) included CTV70, CTV60 and bilateral elective lymph nodes. The margin of 3 mm was added for each CTV to create the planning target volumes (PTV) PTV70, PTV60 and PTV50 (during RT delivery daily cone-beam CT (CBCT) for image guidance was used). For high-risk volumes PTV70 and PTV60 the prescribed doses were 70 Gy and 60 Gy respectively, for PTV50 – 50 Gy. Three metabolic parameters (SUV_{max}, MTV and TLG) were measured in pre-ICT and post-ICT ^{18}F-FDGPET/CT scans for both primary tumour and metastatic regional lymphnodes.

2.4 Chemoradiotherapy

CRT consisted of cisplatin 40 mg/m^2 weekly concomitant with conventionally fractionated RT (2 Gy per once-daily fraction, 5 days a week until the total prescribed dose of 70 Gy will be collected) [19, 20]. The cisplatin dose was individually modified according to the level of hematologic toxicity, hepatic and renal function and the infectious diseases. Non-completion of prescribed radiotherapy dose was related to individual patient tolerance.

2.5 End points

PFS and OS were used as the clinical endpoints to evaluate the feasibility of ^{18}F-FDG PET/CT-based post-ICT GTV delineation and the prognostic value of the ^{18}F-FDG PET metabolic parameters. PFS was defined as the time from day 1 of the ICT first cycle until disease progression or death from any reason. OS was defined as the period from day 1 of the ICT first cycle until death from any reason. Furthermore, to

evaluate the safety of new target volume delineation technique, treatment toxicity during ICT and CRT was weekly evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) v.4.0. Late adverse events related with RT were assessed every three months after CRT using RTOG (Radiation Therapy Oncology Group) /EORT (European Organization for Research and Treatment of Cancer) toxicity criteria.

2.6 Analysis of loco-regional failure patterns

Diagnostic CT or PET/CT documenting recurrence was co-registered with planning CT using rigid image registration technique. Loco-regional failures were classified depending on the percentage volume which received in total 95% of prescribed dose: failures were classified as "in-field" (>95%), "marginal" (≥20%; ≤95%) and "out-field" (<20%) [21, 22]. Mean dose and maximum dose to the failure volume were estimated.

2.7 Statistics

Means of pre-ICT, post-ICT and percentage decrease of SUV_{max}, MTV and TLG were compared between ICT-responder versus ICT-non-responder groups using Mann-Whitney U-test. ROC curve analysis was applied to identify the best discriminating cut-off values for SUV_{max}, MTV, and TLG to predict PFS and OS. Appropriate cut-off was defined as the point on the curve nearest to the upper left corner of the receiver operating characteristics (ROC) graph. The area under the curve (AUC) was used to evaluate the accuracy of the metabolic parameters as a prognostic factor. A Cox proportional hazards regression model was applied to determine the effect of potential factors that were found significant on univariate and multivariate analysis. All tests were two-sided, and the significance threshold was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS 22.0 (Statistical Package for Social Sciences 22.0 for Windows) statistical software.

3. Results

3.1 Patient characteristics

In total 53 patients (50 males and 3 females) with mean age at diagnosis of 55.8 ± 8.9 (range 30 - 71) years were enrolled in this study. As demonstrated in flow diagram of study participants (Figure 1), 47 patients completed ICT and CRT and were eligible for further analysis. 21 (44.7%) of analysed patients had primary hypopharyngeal carcinoma and 26 (55.3%) - oropharyngeal carcinoma (all cases negative for human papillomavirus). Patient characteristics at the time of diagnosis are listed in Table 1.

Figure 1. Flow diagram of study participants

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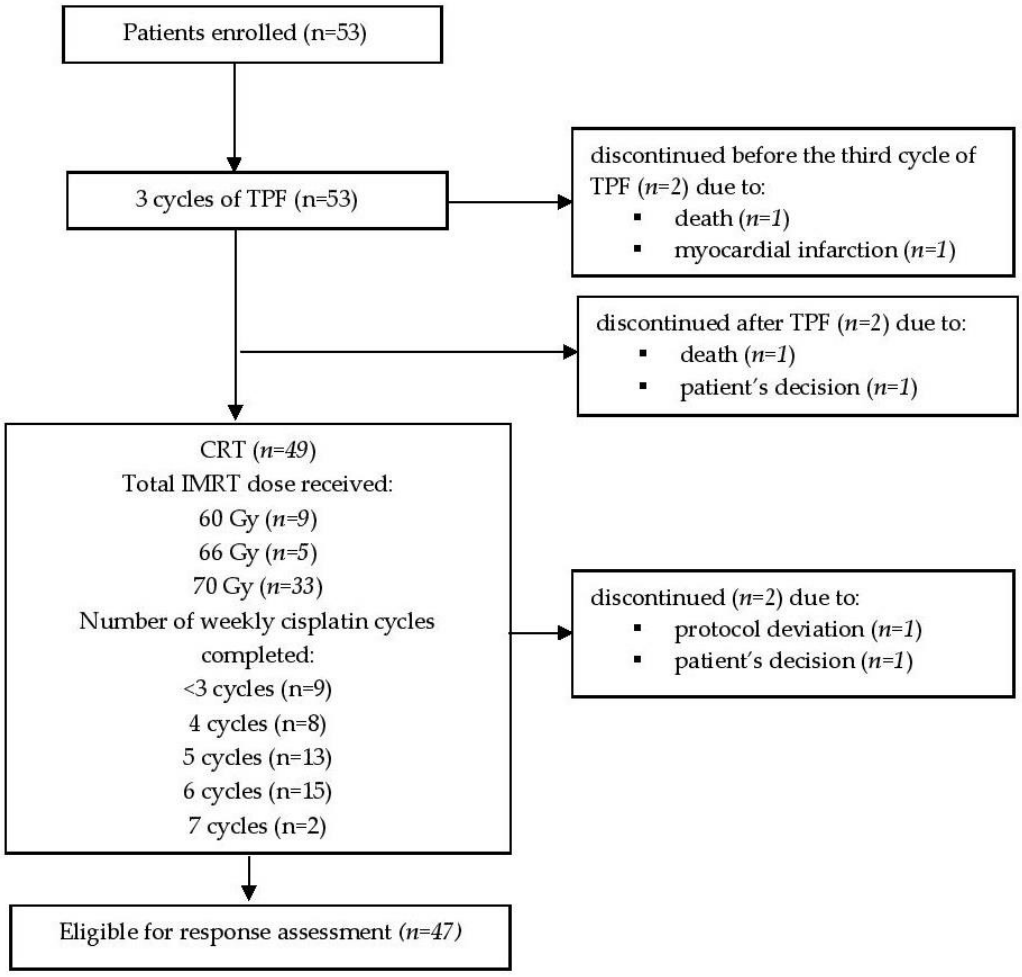

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155 TPF – induction chemotherapy consisting of docetaxel, cisplatin, and 5-fluorouracil (5-FU); IMRT –
156 intensity modulated radiation therapy; CRT – chemoradiotherapy.

157 **Table 1.** Baseline patient and tumour characteristics

Characteristics	n (%)
Age (years)	
Median (range)	55.5 (30-71)
Sex	
Male	45 (95.7%)
Female	2 (4.3%)
ECOG	
0	30 (63.8%)
1	17 (36.2%)
Primary tumour site	
Oropharynx	26 (55.3%)
Hypopharynx	21 (44.7%)

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Tumour status (T)	
T1	0
T2	14 (29.8%)
T3	9 (19.1%)
T4	24 (51.1%)
Lymph node status (N)	
N0	3 (6.4%)
N1	9 (19.1%)
N2	32 (68.1%)
N3	3 (6.4%)
Tumour stage	
III	7 (14.9%)
IV	40 (85.1%)
Histological grade	
G1	1 (2.1%)
G2	27 (57.4%)
G3	19 (40.5%)
G4	0

ECOG - Eastern Cooperative Oncology Group performance status.

3.2 Clinical outcome of 18F-FDG PET/CT-based post-ICT GTV delineation strategy

Median follow-up of patients was 36.4 months (range: 9.7 - 57.2). 3-year PFS and OS rates for all study population were 67% and 61% respectively. According to post-ICT ^{18}F-FDG PET/CT, 10 (21.3%) patients were ICT-non-responders and 37 (78.7%) - ICT-responders. The 3-year PFS for ICT-non-responders was 20%, comparing with 84% for ICT-responders (Hazard ratio (HR) = 6.5, 95% CI 2.33-18.7; p = 0.001) (Figure 2). The 3-year OS for ICT-non-responders was 16% *vs*.78% for ICT-responders (HR = 5.47, 95% CI 2.33-12.83; p = 0.001) (Figure 3). The median PFS and OS were not reached.

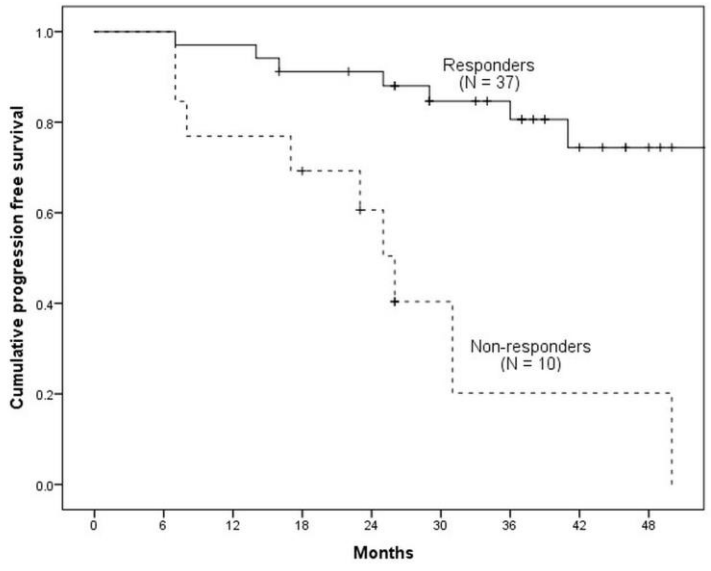

Figure 2. Comparison of PFS between ICT-responders and non-responders

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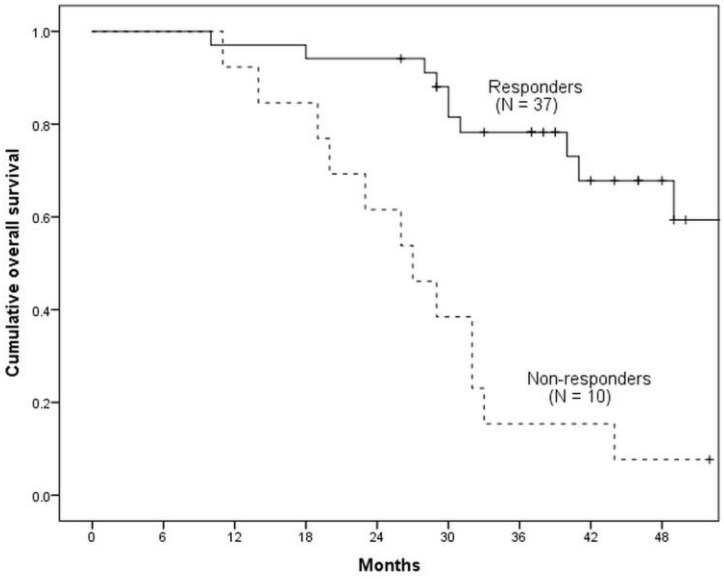

Figure 3. Comparison of OS between ICT-responders and non-responders

3.3 Patterns of loco-regional failures

Loco-regional disease failure occurred in 15 patients (31.9%) (7 in ICT-responder group and 8 in ICT-non-responder group). For 5 patients (10.6%) it was allocated at the primary tumour site, 7 patients (14.9%) had local control but regional failure and 3 patients (6.4%) had both primary and nodal failure. These 15 patients with 32 failures were analysed. Relative to the percentage target volume that received 95% of the prescribed dose for specific PTV, total of 19 (59.3%) failures were classified as in-field, 7 (21.9%) failures were defined as marginal and 6 (18.8%) failures as out-field. The average mean (±standard deviation (SD)), minimum, maximum dose and dose to 95% of planning target volume (D95) delivered to all failures were 63.7 ± 4.9, 59.7 ± 8, 68 ± 3.3 and 62 ± 7.6.

The primary tumour persisted or recurred at the site of high-dose GTV (GTV70) and high-dose CTV (CTV70) in 7 (87.5%) cases, and 1 (12.5%) case occurred in high-dose PTV (PTV70). The failure of LN observed in intermediate-dose GTV (GTV60) and intermediate-dose CTV (CTV60) in 21 (87.5%) cases, and 3 (12.5%) cases in intermediate-dose PTV (PTV60). No failures were observed in prophylactic dose PTV (PTV50) (Table 2).

Table 2. Sites of loco-regional failures and RT doses

Characteristic	Failures (%)		Doses average (± SD)			
	Primary site	LN	Mean dose	Minimum dose	Maximum dose	D95
Type						
In-field	5 (62.5%)	14 (58.3%)	65.1 ± 3.50	62.7 ± 3.6	68.1 ± 3.3	64.05 ± 3.8
Marginal	1 (12.5%)	7 (29.2%)	60.1 ± 8.50	54.2 ± 12	69.1 ± 3.0	57.22 ± 12.8
Out-field	2 (25%)	3 (12.5%)	63.0 ± 3.14	56.3 ± 10	66.7 ± 3.5	60.34 ± 9
Localisation						
GTV */**	5 (62.5%)*	14 (58.3%)**	65.4 ± 3.5	63.5 ± 3.8	67.9 ± 3.1	64.60 ± 3.8
CTV */**	2 (25%)*	6 (25%)**	65.8 ± 3.4	57.7 ± 9.1	67.3 ± 3.3	61.47 ± 8.24

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PTV */**	1 (12.5%)**	4 (16.7%)**	53.8 ± 8.5	50.0 ± 13.1	66.9 ± 3.4	53.10 ± 14.1

*high-dose (70Gy) GTV, CTV and PTV of primary site failures; **intermediate-dose (60Gy) GTV, CTV and PTV of lymph nodes failures; LN - regional lymph nodes

Our study demonstrates that GTV or CTV (GTV + 5mm) encompasses the vast majority of failures.

3.4 Toxicities

During CRT the rates of grade 3 - 4 dermatitis, mucositis, anaemia, leukopenia and thrombocytopenia were 27.6%, 21.2%, 6.4%, 6.4% and 6.4%, respectively. No grade 3 or 4 xerostomia or body-weight loss were observed. The incidence of grade 3 - 4 late toxicities was: 1 (2.1%) patient developed osteoradionecrosis, 1 (2.1%) developed trismus, 2 (4.3%) dysphagia and 1 (2.1%) bleeding.

3.5 ROC Curve analysis, AUC and cut-off values of the metabolic parameters

The mean of SUV_{max} percentage decrease of the primary lesions after ICT was 58.9 ± 24.7% and the mean of MTV and TLG percentage decrease of the primary lesions were 63.4 ± 33.6% and 66.3 ± 41.2% respectively. The mean of SUV_{max}, MTV and TLG percentage decrease of metastatic LN were 38.5 ± 32.8%, 38.5 ± 32.8% and 64.9 ± 34.6% respectively. The abilities of the SUVmax, MTV, and TLG post-ICT percentage decrease values to predict PFS and OS were calculated by ROC curves. AUC of the tested parameters, their optimal cut-off values for PFS and OS are demonstrated in Table 3.

Table 3. AUC and cut-off values of metabolic parameters

Parameter			PFS			OS		
			AUC	Optimal cut-off	Sensitivity/ Specificity	AUC	Optimal cut-off	Sensitivity/ Specificity
Primary tumour	percentage decrease of:	SUV_{max}	0.79	74%	68% / 88%	0.70	74%	69% / 67%
		MTV	0.83	68%	71% / 88%	0.76	69%	76% / 78%
		TLG	0.78	76%	74% / 88%	0.78	74%	74% / 81%
Metastatic LN	percentage decrease of:	SUV_{max}	0.72	68.%	68% / 89%	0.68	69%	69% / 67%
		MTV	0.58	-	-	0.50	-	-
		TLG	0.79	74%	62% / 87%	0.71	73%	72% / 69%

AUC - area under the curve; LN – regional lymphnodes; PFS – progression-free survival; OS – overall survival.

3.6 Prognostic value of the metabolic parameters

Associations of three metabolic ^{18}F-FDG PET/CT parameters SUV_{max}, MTV and TLG in primary tumour and metastatic nodes with post-ICT tumour volume reduction are demonstrated in the Table 4 and Table 5. Tumour response was associated with primary tumour parameters: pre-ICT MTV ($p<0.001$) and TLG ($p=0.02$); post-ICT SUV_{max} ($p=0.004$), MTV ($p<0.001$) and TLG ($p<0.001$); percentage decrease of SUV_{max} ($p=0.027$) and MTV ($p=0.001$). Tumour response was also statistically significantly linked with metastatic LN parameters: pre-ICT MTV ($p<0.001$) and TLG ($p<0.001$); post-ICT MTV ($p=0.006$) and TLG ($p<0.001$). Percentage decrease of LN metabolic parameters was not associated with tumour response.

Table 4. Associations of ^{18}F-FDG PET/CT metabolic parameters with tumour response to ICT in primary tumour

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Parameter of the primary tumour		Total Mean ± SD	ICT-Responders Mean ± SD	ICT-Non-responders Mean ± SD	p value
Pre-ICT	SUV_{max}	17.9 ± 5.8	17.6 ± 1.1	18.9 ± 1.4	0.910
	MTV	34.6 ± 26.6	27.7 ± 3.3	52.7 ± 9.7	<0.001
	TLG	232.3 ± 209.2	178 ± 24.1	372 ± 77.5	0.020
Post-ICT	SUV_{max}	7.2 ± 5.02	3.1 ± 0.9	5.9 ± 3.5	0.004
	MTV	11.8 ± 15.7	6.04 ± 6.9	27.04 ± 21.7	<0.001
	TLG	60.05 ± 91.11	27.2 ± 56.2	146 ± 110	<0.001
Percentage decrease (%)	SUV_{max}	58.9 ± 24.7	68.3 ± 2.7	34.6 ± 7.2	0.027
	MTV	63.4 ± 33.6	74.4 ± 3.2	34.7 ± 12.2	0.001
	TLG	66.3 ± 41.2	68.3 ± 2.7	34.6 ± 7.2	0.950

SUV_{max} – maximum standard uptake value; MTV - metabolic tumour volume; TLG - total lesion glycolysis; SD – standard deviation; ICT – induction chemotherapy.

Table 5. Associations of ^{18}F-FDG PET/CT metabolic parameters with tumour response to ICT in metastatic LN

Parameter of the metastatic LN		Total Mean ± SD	ICT-Responders Mean ± SD	ICT-Non-responders Mean ± SD	p value
Pre-ICT	SUV_{max}	13.02 ± 6.4	12.4 ± 1.1	14.9 ± 1.9	0.820
	MTV	19.3 ± 28.2	12.1 ± 2.4	40.9 ± 13	< 0.001
	TLG	140.3 ± 234.9	77.1 ± 15	330.2 ± 109.7	< 0.001
Post-ICT	SUV_{max}	7.5 ± 5.7	3.3 ± 1.8	5.5 ± 2.5	0.115
	MTV	50.5 ± 129.2	24.1 ± 58.5	129.54 ± 227.2	0.006
	TLG	60.05 ± 91.11	27.2 ± 56.2	146 ± 110	< 0.001
Percentage decrease (%)	SUV_{max}	38.5 ± 32.8	44 ± 5.7	22.2 ± 7.3	0.340
	MTV	38.5 ± 32.8	62 ± 4.7	39.1 ± 12.2	0.211
	TLG	64.9 ± 34.6	72.3 ± 4.3	42.9 ± 13.4	0.090

SUV_{max} – maximum standard uptake value; MTV - metabolic tumour volume; TLG - total lesion glycolysis; SD – standard deviation; LN – regional lymphnodes.

According to the univariate Cox regression analysis (Table 6 and Table 7), percentage decrease of primary tumour SUVmax ≥74%, MTV ≥69%, TLG ≥74%, metastatic LN SUVmax ≥68% and TLG ≥74% and lymphnode status N were significant prognostic factors for both PFS and OS.

In multivariate analysis (Table 6 and Table 7) primary tumour SUVmax decrease ≥74% (HR = 2.7; 95% CI 1.3-5.7; p = 0.03), primary tumour MTV decrease ≥68% (HR = 1.7; 95% CI 0.5-5.4; p = 0.04), primary tumour TLG decrease ≥76% (HR = 3.7; 95% CI 1.2-11.7; p = 0.02), LN TLG decrease ≥74% (HR = 2.8; 95% CI 0.6-6.9; p = 0.03) and N stage (HR = 2.8; 95% CI 0.6-7.2; p = 0.03) remained significantly associated with PFS. Moreover, ≥74% decrease in primary tumour SUVmax (HR = 2.1; 95% CI 0.9-8.7; p = 0.04), ≥69% decrease in primary tumour MTV (HR = 2; 95% CI 0.4-8.2; p = 0.04), ≥74% decrease in primary tumour TLG (HR =

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3.2; 95% CI 0.8-11.4; p = 0.02), ≥73% decrease in LN TLG (HR = 2.6; 95% CI 0.2-6.2; p = 0.02) and N stage (HR = 2.2; 95% CI 0.7-6.1; p = 0.02) remained independent prognostic factors for OS.

Table 6. Univariate and multivariate Cox proportional hazards regression analysis for PFS

Parameter		Cut-off value	Univariate			Multivariate		
			HR	95%CI	p value	HR	95%CI	p value
Primary tumour percentage decrease of:	SUV_{max}	<74 *vs.* ≥74%	2.7	0.7 – 4.2	0.02	2.7	1.3 – 5.7	0.03
	MTV	<68 *vs.* ≥68%	1.5	1.3 - 9.5	0.01	1.7	0.5 – 5.4	0.04
	TLG	<76 *vs.* ≥76%	4.9	1.8 - 13.6	0.002	3.7	1.2 – 11.7	0.02
Metastatic LN percentage decrease of:	SUV_{max}	<68 *vs.* ≥68%	1.2	0.5 – 2.7	0.04	0.7	0.2 – 2.7	NS
	MTV	*	-	-	-	-	-	-
	TLG	<74 *vs.* ≥74%	1.6	0.6 – 3.7	0.03	2.8	0.6 – 6.9	0.03
Tumour status (T)		T2+T3 *vs.* T4	0.9	0.5 – 2.3	NS	-	-	-
Lymphnode status (N)		N0-1 *vs.* N2-3	1.8	0.7 – 1.8	0.02	2.8	0.6 – 7.2	0.03
Tumour site		Oropharynx *vs.* hypopharynx	0.7	0.3 – 1.7	NS	-	-	-
Histological grade		G1-2 *vs.* G3	0.3	0.24-1.4	NS	-	-	-

SUV_{max} – maximum standard uptake value; MTV - metabolic tumour volume; TLG - total lesion glycolysis; LN – regional lymphnodes; * - no optimal cut-off value; NS – not significant.

Table 7. Univariate and multivariate Cox proportional hazards regression analysis for OS

Parameter		Cut-off value	Univariate			Multivariate		
			HR	95%CI	p value	HR	95%CI	p value
Primary tumour percentage decrease of:	SUV_{max}	<74 *vs.* ≥74%	2.5	1 – 6.2	0.03	2.1	0.9 – 8.7	0.04
	MTV	<69 *vs.* ≥69%	1.9	0.8 – 5.2	0.04	2	0.4 – 8.2	0.04
	TLG	<74 *vs.* ≥74%	3.2	1.3 – 7.7	0.01	3.2	0.8 – 11.4	0.02
Metastatic LN percentage decrease of:	SUV_{max}	<69 *vs.* ≥69%	1.4	0.5 – 3.2	0.02	0.8	0.9 – 4.0	NS
	MTV	*	-	-	-	-	-	-
	TLG	<73 *vs.* ≥73%	2.2	0.9 – 6.6	0.02	2.6	0.2 – 6.2	0.02
Tumour status (T)		T2+T3 *vs.* T4	0.8	0.6 – 3.4	NS	-	-	-
Lymphnode status (N)		N0-1 *vs.* N2-3	1.8	0.6 – 5.4	0.03	2.2	0.7 – 6.1	0.02
Tumour site		Oropharynx *vs.* hypopharynx	0.7	0.3 – 1.7	NS	-	-	-
Histological grade		G1-2 *vs.* G3	0.6	0.2 – 1.4	NS	-	-	-

SUV_{max} – maximum standard uptake value; MTV - metabolic tumour volume; TLG - total lesion glycolysis; LN – regional lymphnodes; * - no optimal cut-off value.

4. Discussion

Our study is the first to investigate the feasibility of target volume delineation based on post-ICT ^{18}F-FDG PET/CT images for LA-SCCHN IMRT planning. The rationale for this approach is the potential reduction of GTV after ICT leading to mitigation of RT toxicities by sparing normal tissues. Several authors in their publications have discussed post-ICT imaging-based target volume delineation strategy [6,8,9,23].

However, due to the lack of supportive data they still recommend the use of pre-induction primary tumour and nodal GTVs but further clinical research is needed.

Survival data from our study cannot be directly compared with the results of other authors because there are no completed clinical trials analysing post-ICT PET/CT based RT planning. For indirect comparison patients' outcomes of several clinical studies, where ICT plus CRT approach was used for LA-SCCHN treatment are presented in Table 8. One of the earliest published studies analysing LA-SCCHN patients treated with ICT (TPF) plus CRT was TAX-324 [24]. In this study 3-year PFS and OS rates were 50% and 62% respectively. In the PARADIGM study published by Haddad et al., patients in ICT arm received 3 cycles of TPF plus CRT with weekly carboplatin, 67% of patients were progress free and 73% were alive in 3 years after treatment [4]. Takacsi-Nagy et al. in phase II clinical trial involving 66 LA-SCCHN patients demonstrated that after 2 cycles of TPF followed by CRT (total dose of 70 Gy in 7 weeks with 3 concurrent cycles of cisplatin on days 1, 22 and 43 of radiotherapy) 3-year PFS rate was 41% and OS rate - 43% [25]. Ghi et al. analysed 208 patients randomised for either CRT with cisplatin (n=129) or radiotherapy with cetuximab (n=79) after initial 3 cycles of TPF [26]. 3-year PFS and OS rates were 47% and 57.5% respectively. In our study, involving 47 patients treated with 3 cycles of TPF plus CRT (70 Gy in 7 weeks with weekly cisplatin 40 mg/m2), we demonstrated 3-year PFS rates of 67% and 3-year OS rates of 61%. Summarizing the data, 3-year PFS and OS rates in our study were non-inferior comparing to survival results in studies with the standard treatment approach.

Table 8. Patient survival data in previous studies with ICT plus CRT approach and in our study

Study	Eligibility	Patients	Study design	3-year OS rates	3-year PFS rates
Lorch et al. [24]	Stage III-IV	501	TPFx3, SRT+CBP weekly vs. CP/5-Fu, SRT+CBP weekly	62%	50%
Haddad et al. [4]	Stage III-IV	145	TPFx3, SRT+CBP weekly vs. HRT+CPx2	73%	67%
Takacsi-Nagy et al. [25]	Stage III-IV	66	TPFx2, SRT+CPx3 vs. CRT	43%	41%
Ghi et al. [26]	Stage III-IV	413	TPFx3, SRT+CPx2 vs. SRT+CTX	57.5%	47%
Our study	Stage III-IV	47	TPFx3, SRT+CP weekly	61%	67%

TPF: docetaxel, cisplatin, 5-Fluorouracil; SRT: single daily fraction radiotherapy; HRT: hyperfractionated radiotherapy; CBP: carboplatin; CP: cisplatin: CTX: cetuximab; CRT: chemoradiotherapy; 5-FU: 5-fluorouracil.

According to the survival data presented above, we suggest that 18F-FDG PET/CT scan obtained after TPF-based ICT might be used for LA-SCCHN IMRT planning. Loco-regional failure analysis also supports this approach. In our study 15 patients (31.9%) developed loco-regional disease progression with a total of 32 progressive lesions. 8 lesions were in the primary tumour site and 24 in the regional lymphnode sites. 90.6% of progresses were in-field with highest levels localised in high-to-intermediate risk volumes GTV70 (87.5%) and CTV60 (87.5%) and none in PTV50 volume. For comparison, De Felice et al. presented the retrospective analysis of 56 patients who were diagnosed with loco-regional progress of LA-SCCHN after ICT plus CRT [21]. In total 68 sites of progression were analysed, of them 35 were in primary tumour site and 33 in regional nodes. 95.6% of progressive lesions were in-field, 82.9% in high-dose primary tumour CTV (GTV + 10 mm), and 72.7% in nodal high-dose CTV. Similar results were demonstrated by Baymanet al. [27]. Study involved 136 patients with carcinoma of the head and neck. 29 (21%) patients were treated

with ICT plus CRT. 16 (12%) of patients progressed, all in high-dose region. The main difference between the studies mentioned above and our study is GTV to CTV margin. In both earlier studies CTV was defined as GTV plus 10mm margin and PTV – CTV plus 4mm. In our study smaller 5mm GTV to CTV margin and 3mm CTV to PTV margin (accounting for daily CBCT image guidance) was used. We want to point-out that despite the smaller margins, results of loco-regional control were similar to previous studies, therefore we suggest that 5mm CTV and 3mm PTV margins (with daily CBCT image guidance) might be considered for 18F-FDG PET/CT based IMRT planning after ICT for LA-SCCHN patients.

In recent years several authors demonstrated a prognostic value of 18F-FDG PET/CT metabolic parameters in LA-SCCHN [15,16,28-30]. In publication by Paidpally et al. SUVmax, MTV and TLG were proposed as non-invasive prognostic factors usable in management of LA-SCCHN [28]. These parameters might be used for disease response evaluation, RT planning and follow-up. David et al. analysed 74 LA-SCCHN patients with N2 or N3 nodal status [15]. SUVmax, SUVpeak (mean SUV within a 1-cm sphere centered on SUVmax) of the primary tumour and LN were evaluated before and after treatment. Neither initial nor post-treatment SUVmax and SUVpeak were associated with disease outcome. Choosing the different approach and analysing the dynamics of SUVmax (percentage decrease of the value after ICT) on patient survival, we provide new evidence that the decrease of primary tumour SUVmax by at least 74% and LN SUVmax by 68-69% may be used as independent LA-SCCHN prognostic factors. However, our results contradict with the results of Yu et al., who did not find an association between SUVmax percentage decrease and LA-SCCHN patient survival [16].

Few authors also investigated the prognostic value of MTV and TLG. In the study of David et al., pre-treatment MTV value was linked with PFS and OS [15]. Yu et al. found that post-ICT MTV percentage decrease by more than 42% and TLG by more than 55% significantly prolonged event-free survival [16]. In our study it was found that larger percentage decrease of MTV and TLG in primary tumour and TLG in regional LN correlate with better 3-year PFS and OS rates, however different cut-off points were established. MTV percentage decrease cut-off point for PFS prediction was 68%, for OS 69%. Only primary tumour MTV decrease was significantly associated with disease outcome. As for TLG better PFS was observed in patients with ≥76% primary tumour TLG decrease and ≥74% nodal TLG decrease with similar results for OS - ≥74% and ≥73% decrease respectively.

Results of this phase II cohort study demonstrate that post-ICT ^{18}F-FDG PET/CT based RT planning has no negative impact on loco-regional recurrence rates comparing with the patterns to pre-ICT imaging-based treatment planning (demonstrated by others authors). In order to improve the analysis of loco-regional progression and assess the future possibility of dose escalation in high-risk volumes we are initiating a 3D-printed phantom prototype filled with radiosensitive gels-based dosimetry for individual patient dosimetry according to RT plans. After completion of pre-planned investigations, we hope to propose more biologically adapted radiation therapy techniques for LA-SCCHN patients expecting for better loco-regional control and individually advanced patient dosimetry. Further prospective studies with larger sample sizes are warranted to confirm the ^{18}F-FDG-PET/CT based post-ICT target volume delineation technique before its use in clinical practice. Also, we encourage larger validation studies of metabolic ^{18}F-FDG-PET/CT prognostic markers.

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6. Author contributions

Conceptualization V.R., M.R.; Methodology V.R., S.Š. and I.K.; Investigation V.R, E.K., S.Š., E.P., N.J. and E.JA.; Data curation V.R., M.R., E.K., E.P. and S.Š.; Original Draft Preparation V.R., E.K., E.JA., D.A., N.J.; Review and Editing I.K.; D.A., E.J; Supervision; I.K., D.A., E.J.;. All authors read and approved the final manuscript.

7. Conflicts of interest

The authors declare no conflict of interests. The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

References

1. Benasso, M. Induction chemotherapy for squamous cell head and neck cancer: A never ending story? *Oral Oncol* **2013**, *49*, pp. 747-752, DOI: 10.1093/annonc/mdt461.
2. Hitt, R.; Grau, J.J.; López-Pousa, A.; Berrocal, A.; García-Girón, C.; Irigoyen, A.; Sastre, J.; Martínez-Trufero, J.; Brandariz Castelo, J.A.; Verger, E., Cruz-Hernández, J.J.; Spanish Head and Neck Cancer Cooperative Group (TTCC). A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and cancer. *Ann Oncol* **2014**, *25*, pp. 216-225, DOI: 10.1093/annonc/mdt461.
3. Cohen, E.E.W.; Karrison, T.; Kocherginsky, M.; Mueller, J.; Egan, R.; Huang, C.H.; Brockstein, B.E.; Agulnik, M.B.; Mittal, B.B.; Yunus, F.; Samant, S.; Raez, L.E.; Mehra, R.; Kumar, P.; Ondrey ,F.; Marchand, P.; Braegas, B.; Seiwert, T.Y.; Villaflor, V.M.; Haraf, D.J.; Vokes, E.E. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol* **2014**, *32*, pp. 2735-2743, DOI: 10.1200/JCO.2013.54.6309.
4. Haddad, R.I.; Rabinowits, G.; Tishler, R.; Khuri, F.; Adkins, D.; Clark, J.; Sarlis, N.; Lorch, J.; Beitler, J.J.; Limaye, S.; Riley, S.; Posner, M. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol* **2013**, *14*, pp. 257-264, DOI: 10.1016/S1470-2045(13)70011-1.
5. Powell, C.; Schmidt, M.; Borri, M.; Koh, D.M.; Partridge, M.; Riddell, A.; Cook, G.; Bhide, S.A.; Nutting, C.M.; Harrington, K.J.; Newbold, K.L. Changes in functional imaging parameters following induction chemotherapy have important implications for individualized patient-based treatment regimens for advanced head and neck cancer. *Radiother Oncol* **2013**, *106*, pp.112-117, DOI: 10.1016/j.radonc.2012.09.009.
6. Salama, J.K.; Haddad, R.I.; Kies, M.S.; Busse, P.M.; Dong, L.; Brizel, D.M.; Eisbruch, A.; Tishler, R.B.; Trotti, A.M.; Garden, A.S. Clinical practice guidance for radiotherapy planning after induction chemotherapy in locoregionally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* **2009**, *75*, pp. 725-733, DOI: 10.1016/j.ijrobp.2008.11.059.

7. Vicente, A.M.G.; Castrejón, A.S.; Londoño, G.A.J. PET/CT in radiotherapy planning in head and neck cancers. *Médecine Nucléaire* **2015**, *39*, pp. 465-470, DOI: 10.1016/j.mednuc.2015.06.001.
8. Grégoire, V.; Evans, M.; Le, Q.T.; Bourhis, J.; Budach, V.; Chen, A.; Eisbruch, A.; Feng, M.; Giralt, J.; Gupta, T.; Hamoir, M.; Helito, J.K.; Hu, C.; Hunter, K.; Johansen, J.; Kaanders, J.; Laskar, S.G.; Lee, A.; Maingon, P.; Mäkitie, A.; Micciche', F.; Nicolai, P.; O'Sullivan, B.; Poitevin, A.; Porceddu, S.; Składowski, K.; Tribius, S.; Waldron, J.; Wee, J.; Yao, M.; Yom, S.S.; Zimmermann, F.; Grau, C. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. *Radiother Oncol* **2018**, *126*, pp. 3-24, DOI: 10.1016/j.radonc.2017.10.016.
9. Francesca, De F.; Daniela, M.; Vincenzo, T. Target volume delineation after induction chemotherapy in locally advanced head and neck cancer. *Oral oncol* **2015**, *51*, pp. e81, DOI: 10.1016/j.oraloncology.2015.09.005.
10. Doornaert, P.; Dahele, M.; Verbakel, W.F.; Bohoudi, O.; Slotman, B.J.; Langendijk, J.A. The effect of induction chemotherapy on tumor volume and organ-at-risk doses in patients with locally advanced oropharyngeal cancer. *Radiother Oncol* **2013**, *109*, pp. 269-274, DOI: 10.1016/j.radonc.2013.07.016.
11. Newbold, K.; Powell, C. PET/CT in radiotherapy planning for head and neck cancer. *Front Oncol* **2012**, *2*, pp. 189, DOI: 10.3389/fonc.2012.00189.
12. Kawakita, D.; Masui, T.; Hanai, N.; Ozawa, T.; Hirakawa, H.; Terada, A.; Nishio, M.; Hosoi, H.; Hasegawa, Y. Impact of positron emission tomography with the use of fluorodeoxyglucose on response to induction chemotherapy in patients with oropharyngeal and hypopharyngeal squamous cell carcinoma. *Acta Otolaryngol* **2013**, *133*, pp. 523-530, DOI: 10.3109/00016489.2012.733411.
13. Abgral, R; Le Roux, P.Y.; Keromnes, N.; Rousset, J.; Valette, G.; Gouders, D.; Leleu, C.; Mollon, D.; Nowak, E.; Querellou, S.; Salaün, P.Y. Early prediction of survival following induction chemotherapy with DCF (docetaxel, cisplatin, 5-fluorouracil) using FDG PET/CT imaging in patients with locally advanced head and neck squamous cell carcinoma. *Eur J Nucl Med Mol Imaging* **2012**, *39*, pp.1839-1847, DOI: 10.1007/s00259-012-2213-x.
14. Gavid, M.; Prevot-Bitot, N.; Timoschenko, A.; Gallet, P.; Martin, C.; Prades, J.M. [18F]-FDG PET-CT prediction of response to induction chemotherapy in head and neck squamous cell carcinoma: preliminary findings. *Eur AnnOtorhinolaryngol Head Neck Dis* **2015**, *132*, pp. 3-7, DOI: 10.1016/j.anorl.2014.01.009.
15. Schwartz, D.L.; Harris, J.; Yao, M; Rosenthal, D.I.; Opanowski, A.; Levering, A.; Ang, K.K.; Trotti, A.M.; Garden, A.S.; Jones, C.U.; Harari, P.; Foote, R.; Holland, J.; Zhang, Q.; Le, Q.T. Metabolic tumor volume as a prognostic imaging-based biomarker for head-and-neck cancer: pilot results study from radiation therapy oncology group protocol 0522. *Int J RadiatOncolBiol Phys* **2015**, *91*, pp. 721-729.
16. Yu, J.; Cooley, T.; Truong, M.T.; Mercier, G.; Subramaniam, R.M. Head and neck squamous cell cancer (stages III and IV) induction chemotherapy assessment: value of FDG volumetric imaging parameters. *J Med Imaging RadiatOncol* **2014**, *58*, pp. 18-24, DOI: 10.1111/1754-9485.12081.

17. Yoon, D.H.; Cho, Y.; Kim, S.Y.; Nam, S.Y.; Choi, S.H.; Roh, J.L.; Lee, S.W.; Song, S.Y.; Lee, J.H.; Kim, J.S.; Cho, K.J.; Kim, S.B. Usefulness of interim FDG-PET after induction chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck receiving sequential induction chemotherapy followed by concurrent chemoradiotherapy. *Int J RadiatOncolBiol Phys* **2011**, *81*, pp.118-125, DOI: 10.1016/j.ijrobp.2010.04.034.
18. Vermorken, J.B.; Remenar, E.; Herpen, C.; Gorlia, T.; Mesia, R.; Degardin, M.; Stewart, J.S.; Jelic, S.; Betka, J.; Preiss, J.H.; van den Weyngaert, D.; Awada, A.; Cupissol, D.; Kienzer, H.R.; Rey, A.; Desaunois, I.; Bernier, J.; Lefebvre, J.L.; EORTC 24971/TAX 323 Study Group. Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer. *N Engl J Med* **2007**, *357*, pp. 1695-1704, DOI: 10.1056/NEJMoa071028.
19. Homma, A.; Inamura, N.; Oridate, N.; Suzuki, S.; Hatakeyama, H.; Mizumachi, T.; Kano, S.; Sakashita, T.; Onimaru, R.; Yasuda, K.; Shirato, H.; Fukuda, S. Concomitant Weekly Cisplatin and Radiotherapy for Head and Neck Cancer. *Jpn J ClinOncol* **2011**, 41, pp. 980-986, DOI: 10.1093/jjco/hyr086.
20. Steinmann, D.; Cerny, B.; Karstens, J.H.; Bremer, M. Chemoradiotherapy with Weekly Cisplatin 40 mg/m2 in 103 Head-and-Neck Cancer Patients. *Strahlenther Oncol*, **2009**, *185*, pp.682-688.
21. De Felice, F.; Thomas, C.; Barrington, S.; Pathmanathan, A.; Lei, M.; Urbano, T.G. Analysis of loco-regional failures in head and neck cancer after radical radiation therapy. *Oral Oncol* **2015**, *51*, pp. 1051-1055, DOI: 10.1016/j.oraloncology.2015.08.004.
22. Studer, G.; Luetolf, U.M.; Glanzmann, C. Locoregional failure analysis in head-and- neck cancer patients treated with IMRT. *Strahlenther Onkol* **2007**, *183*, pp. 417-423, DOI: 10.1007/s00066-007-1663-8.
23. Eisbruch, A.; Grégoire, V. Balancing risk and reward in target delineation for highly conformal radiotherapy in head and neck cancer. *Semin Radiat Oncol* **2009**, *19*, pp. 43-52, DOI: 10.1016/j.semradonc.2008.09.008.
24. Lorch, J.H.; Goloubeva, O.; Haddad, R.I.; Cullen, K.; Sarlis, N.; Tishler, R.; Tan, M.; Fasciano, J.; Sammartino, D.E.; Posner, M.R. Long term results of TAX324, a randomized phase III trial of sequential therapy with TPF versus PF in locally advanced squamous cell cancer of the head and neck. *Lancet Oncol* **2011**, *12*, pp. 153–159, DOI: 10.1016/S1470-2045(10)70279-5.
25. Takacsi-Nagy, Z.; Hitre, E.; Remenar, E.; Oberna, F.; Polgár, C.; Major, T.; Gödény, M.; Fodor, J.; Kásler, M. Docetaxel, cisplatin and 5-fluorouracil induction chemotherapy followed by chemoradiotherapy or chemoradiotherapy alone in stage III-IV unresectable head and neck cancer: Results of a randomized phase II study. *Strahlenther Onkol* **2015**, *191*, pp. 635-641, DOI: 10.1007/s00066-015-0829-z.
26. Ghi, M.G.; Paccagnella, A.; Ferrari, D.; Foa, P.; Alterio, D.; Codecà, C.; Nolè, F.; Verri, E.; Orecchia, R.; Morelli, F.; Parisi, S.; Mastromauro, C.; Mione, C.A.; Rossetto, C.; Polsinelli, M.; Koussis, H.; Loreggian, L.; Bonetti, A.; Campostrini, F.; Azzarello, G.; D'Ambrosio, C.; Bertoni, F.; Casanova, C.; Emiliani, E.; Guaraldi, M.; Bunkheila, F.; Bidoli, P.; Niespolo, R.M.; Gava, A.; Massa, E.; Frattegiani, A.; Valduga, F.; Pieri, G.; Cipani, T.; Da Corte, D.; Chiappa, F.; Rulli, E.; GSTTC (Gruppo di Studio Tumori della Testa e del Collo) Italian Study Group. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II–III trial. *Ann Oncol* **2017**, *28*, pp. 2206-2212, DOI: 10.1093/annonc/mdx299.

27. Bayman, E.; Prestwich, R.J.; Speight, R.; Aspin, L.; Garratt, L.; Wilson, S.; Dyker, K.E.; Sen, M. Patterns of failure after intensity-modulated radiotherapy in head and neck squamous cell carcinoma using compartmental clinical target volume delineation. *Clin Oncol (R Coll Radiol)* **2014**, *26*, pp. 636-642, DOI: 10.1016/j.clon.2014.05.001.
28. Paidpally, V.; Chirindel, A.; Lam, S.; Agrawal, N.; Quon, H.; Subramaniam, R.M. FDG-PET/CT imaging biomarkers in head and neck squamous cell carcinoma. *Imaging Med* **2012**, *4*, pp. 633-647, DOI: 10.2217/iim.12.60.
29. Min, M.; Lin. P; Lee, M.; Shon, I.H.; Lin, M.; Forstner, D.; Tieu, M.T.; Chicco, A.; Bray, V.; Fowler, A. 18F-FDG PET-CT performed before and during radiation therapy of head and neck squamous cell carcinoma: Are they independent or complementary to each other? *J Med Imaging Radiat Oncol* **2016**, *60*, pp. 433-440, DOI: 10.1111/1754-9485.12439.
30. Šedienė, S.; Kulakienė, I.; Rudžianskas, V.; Ambrazienė, R. The Role of 18-Fluoro-2-Deoxy-Glucose Positron Emission Tomography/Computed Tomography as Response and Prognosis Predictive Factor of Concurrent Chemoradiotherapy after InductionChemotherapy in Head and Neck Squamous Cell Carcinoma: A Prospective Study. *Medicina* **2018**, *54*, pp. 1-13, DOI: 10.3390/medicina54020031.