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Predictive and prognostic values of pretreatment functional imaging-based biomarkers in advanced-stage laryngeal cancer

Görkem Eskiizmir[1], Gülgün Yılmaz Ovalı[2], Feray Aras[3], Beyhan Cengiz Özyurt[4], Serdar Tarhan[2]

[1]Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[2]Department of Radiology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[3]Department of Nuclear Medicine, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[4]Department of Public Health, Faculty of Medicine, Celal Bayar University, Manisa, Turkey

Abstract

Objective: To determine the quantitative values of apparent diffusion coefficient (ADC), standardized uptake values (SUV_{max}, SUV_{mean}), metabolic tumor volume (MTV), metabolic tumor volume indexes (MTI_{max}, and MTI_{mean}) using diffusion weighted-MRI (DW-MRI) and positron emission tomography/computed tomography (PET/CT), and analyze the predictive and prognostic values of these biomarkers in a homogenous group of patients with advanced-stage laryngeal cancer.

Methods: Patients with newly diagnosed advanced-stage laryngeal cancer who had both DW-MRI and 18F-FDG PET/CT before treatment, and who had curative cancer treatment (surgery ± adjuvant therapy or radio ± chemotherapy) between 2011 and 2015 were included in this study. All patients were followed up clinically and radiologically, if necessary every 3 months for the first 2 years, every 4–6 months for year 3, and then annually thereafter.

Results: Thirty-eight patients were retrospectively analyzed. Our analysis demonstrated statistically significant differences when the pretreatment SUV and MTI_{mean} value were compared between patients with stages III and IV. Standardized uptake value was also a predictive factor for N-stage. Moreover, a statistically significant difference was determined when patients with and without perinodal involvement (PNI) were compared. Log rank analysis demonstrated that none of functional imaging-based biomarkers had a prognostic role for oncological outcomes.

Conclusion: Our results demonstrated that pretreatment SUV and MTI_{mean} values were predictive factors for staging, N-stage and PNI. Indeed, functional imaging-based biomarkers are promising, novel, non-invasive techniques that may provide additional information about tumor characteristics, treatment selection and prognosis in the near future.

Keywords: Predictive, prognostic, imaging-based biomarkers, laryngeal cancer.

Özet: İleri evre larenks kanserinde tedavi öncesi fonksiyonel görüntülemeye dayalı biyobelirteçlerin öngördürücü ve prognostik değeri

Amaç: Difüzyon ağırlıklı MR görüntüleme (DW-MRI) ve pozitron emisyon tomografi/bilgisayarlı tomografiyi (PET/BT) kullanarak görünür difüzyon katsayısının (ADC) nicel değerleri, standardize edilmiş tutulum değeri (SUV_{maks}, SUV_{ort}), metabolik tümör volümü (MTV), metabolik tümör volüm göstergelerini (MTI_{maks} ve MTI_{ort}) belirlemek ve ileri evre larenks kanserli homojen hasta grubunda bu biyobelirteçlerin öngördürücü ve prognostik değerlerini incelemektir.

Yöntem: Yeni tanı konmuş ileri evre larenks kanserli, tedavi öncesi hem DW-MRI hem de 18F-FDG PET/BT çektirmiş ve 2011–2015 yılları arasında küratif kanser tedavisi görmüş (cerrahi ± adjuvan tedavi veya radyoterapi ± kemoterapi) hastalar çalışmaya dahil edildi. Hastaların tümü gerektiğinde ilk 2 yıl 3 ayda bir, 3. yıl 4–6 ayda bir ve daha sonra yılda bir klinik ve radyolojik olarak izlendi.

Bulgular: Otuz sekiz hasta geriye dönük olarak incelendi. İncelememiz evre III ve IV hastalar arasında tedavi öncesi SUV ve MTI_{ort} değerleri açısından istatistiksel açıdan anlamlı farklılıklar olduğunu gösterdi. Standardize edilmiş tutulum değeri evresi de N-evresi için bir öngördürücü faktördü. Ayrıca perinodal tutulumu (PNT) olan ve olmayan hastalar arasında da istatistiksel açıdan anlamlı farklılık olduğu belirlendi. Logaritmik sıralama çözümlemesi, fonksiyonel görüntülemeye dayalı biyobelirteçlerin hiçbirisinin onkolojik sonuçlar açısından prognostik role sahip olmadığını gösterdi.

Sonuç: Bulgularımız tedavi öncesi SUV ve MTI_{ort} değerlerinin evreleme, N-evresi ve PNT açısından öngördürücü faktörler olduğunu göstermiştir. Gerçekten de fonksiyonel görüntülemeye dayalı biyobelirteçler tümörün özellikleri, tedavi seçimi ve yakın dönem prognozu hakkında ek bilgi sağlayan umut verici, yeni ve girişimsel olmayan tekniklerdir.

Anahtar sözcükler: Öngördürücü, prognostik, görüntülemeye dayalı biyobelirteçler, larenks kanseri.

Correspondence: Görkem Eskiizmir, MD., FTBORLHNS, sPh.D. Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Turkey
e-mail: gorkemeskiizmir@yahoo.com

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Laryngeal cancer is one of the most common type of head and neck cancers with an incidence of 5.1–10/100,000 worldwide.[1] In laryngeal cancer, the survival rates are 63– 66% (5-year overall survival (OS) for glottic laryngeal cancer: 77% and 5-year OS for supraglottic laryngeal cancer: 51% for cancer).[2–4] However, the survival rates are suboptimal (≤50%) in patients with advanced-stage laryngeal cancer.[1,2,5–7]

Currently, cross-sectional imaging is of utmost important for accurate staging and treatment planning.[8] Therefore, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are frequently used for the imaging of patients with laryngeal cancer. In clinical practices, CT and/or MRI are generally recommended for the assessment of tumor extension and cervical lymph node involvement.[3,5,9] In addition, PET/CT is useful for the detection of lymph node metastasis, distant metastasis and second primary malignant neoplasms such as lung cancer.[10–13] Remarkably, recent advancements in the field of imaging technologies demonstrate that Diffusion weighted-MRI (DW-MRI) and PET/CT may provide significant additional information which are called as "*functional imaging-based biomarkers*". These biomarkers are promising candidates for the understanding of intrinsic tumor biology and features, and may be helpful for the depiction of tumor microenvironment, prediction of treatment response and prognosis in patients with cancer.[14–17] Briefly, DW-MRI, a form of functional MRI, evaluates the random motion of extracellular H_2O molecules which is quantitatively expressed as *apparent diffusion coefficient* (ADC). In literature, an inverse relationship between ADC values and cell proliferation and density has been reported in different neoplasms such as breast cancers, neuroepithelial tumors and nasopharyngeal cancers.[16,18,19] Moreover, several studies have demonstrated lower ADC values (showing high tumor cellularity) in malignant tumors of head and neck despite of different cut-off values (ranging $0.84–1.455\times10^{-3}$ mm^2/s).[20–26] In addition, PET/CT provides the measurement of different metabolic indexes such as standardized uptake values (SUV) and total lesion glycolysis (TLG), which is measured by metabolic tumor volume indexes (MTI), and volumetric parameters such as metabolic tumor volume (MTV) in several malignant neoplasms including cutaneous malignant melanoma, non-small cell lung cancer, bone and soft tissue sarcomas, brain tumors, breast cancers, renal cell carcinoma, T-cell leukemia, and head and neck cancers.[27–34] However, the predictive and prognostic roles of abovementioned functional imaging-based biomarkers are unknown in patients with advanced-stage laryngeal cancer. Therefore, the purpose of the current study is to determine the quantitative values of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} using DW-MRI and PET/CT, and analyze the predictive and prognostic values of these biomarkers in a homogenous group of patients with advanced-stage laryngeal cancer.

Materials and Methods

This retrospective study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Institutional Ethics Committee.[35]

Study population

The study population involved patients with advanced-stage laryngeal cancer who had curative cancer treatment (surgery ± adjuvant therapy or radio ± chemotherapy) between 2011 and 2015. The exclusion criteria were as follows: (i) patients who had a recurrent tumor, (ii) patients who had a palliative treatment or patients who rejected treatment, and (iii) patients who did not have pretreatment MRI and/or PET/CT. Therefore, all patients were newly diagnosed advanced-stage laryngeal cancer, and had both DW-MRI and 18F-FDG PET/CT before treatment. All patients were followed up clinically and radiologically, if necessary every 3 months for the first 2 years, every 4–6 months for year 3, and then annually thereafter. Any sign of recurrence at primary tumor burden and/or neck was defined as locoregional recurrence. In addition, any metastatic lesion at a solid organ (e.g. lung, liver, bone, etc.) was accepted as distant metastasis.

MRI acquisition

All MRI examinations were performed on a 1.5 Tesla scanner (Signa Excite HDX; General Electric Healthcare, Milwaukee, WI, USA). All patients also had conventional neck MRI before DW-MRI. Diffusion weighted-MRI was obtained with single-shot echo-planar imaging sequences in the axial plane with b=0 and 800 s/mm^2; TR/TE 2000/75 ms; 256×256 matrix; FOV: 230 mm; NEX: 16; 4 mm slice thickness; 0 mm interval. Images were processed in the workstation (Advantage Windows version 4.7; General Electric Healthcare, Milwaukee, WI, USA) with Functool software (General Electric Healthcare, Milwaukee, WI, USA). Apparent diffusion coefficient maps were processed and ADC values were calculated manually by an experienced radiologist (GYO, a European

Neuroradiology and Head and Neck certified specialist who has a 12 years' experience in head and neck imaging), who was blinded to clinical staging and PET-CT data. Contrast enhanced- and STIR images were compared and fusion images were performed with ADC maps to define the whole tumor volume (**Figs. 1a** and **1b**). The regions-of-interests (ROI) included all tumors' volume excluding necrotic parts. Apparent diffusion coefficient mean values and standard deviations were recorded for each patient individually.

18F FDG PET/CT acquisition

All patients acquired whole body and spot F-18 FDG PET/CT (Philips, Medical Systems, Cleveland, OH, USA). All patients were asked to fast for at least 6 hours before scanning. A peripheral blood glucose level of less than 180 mg/dl was confirmed initially, and patients received an intravenous injection of 145 µCi/kg (maximum 200 µCi) of FDG afterwards. All images were obtained from base of skull to mid thigh level (**Fig. 1b**). The SUV_{max} of primary tumor burdens and suspicious lymph node stations were detected automatically by the software after delineation of the ROI on attenuation-corrected PET/CT images. All F-18 FDG PET/CT scans were reevaluated by an author of the study (FA). Standardized uptake values (SUV_{max} and SUV_{mean}), MTV and MTI (MTI_{max} and MTI_{mean}) were calculated from primary tumor by automatic program.

Statistical analysis

All data were evaluated using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The descriptive results about study population and tumor characteristics were determined. Kolmogorov-Smirnov and Shapiro-Wilk tests demonstrated that study population was not normally distributed. Therefore, the predictive roles of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} were evaluated by Mann-Whitney U test. In addition, 2-year OS, locoregional control (LRC) and disease-free survival (DFS) were determined by Kaplan-Meier test. A "*receiver operating characteristic*" analysis was performed for a cut-off value of ADC value, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean}; however, we were unable to determine a value with a high sensitivity and specificity. Therefore, the median values of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} were measured. Thereby, study population was separated into two groups as "*low*" and "*high*" according to the median values of each variable. Thereafter, survival analysis was performed using log rank test. A p-value of <0.05 was accepted statistically significant.

Results

Descriptive statistics

Thirty-eight patients (33 males, 86.8%; 5 females, 13.2%) with advanced-stage laryngeal cancer were retrospectively analyzed. Of these patients, 18 presented with supraglottic carcinoma (47.4%), 5 with glottic carcinoma (13.2%) and 15 with transglottic carcinoma (39.5%). With regard to tumor stage, 19 (50%) patients presented with T3 tumors, 19 (50%) with T4 tumors. The distribution of tumor grades were as follows: 3 patients (7.9 %) with well differentiated tumors, 20 patients (52.6%) with moderately differentiated tumors, 9 patients (23.7%) with poorly differentiated tumors. The mean value of age was 64.4 (range: 47 to 87) years; and only 5 patients were female. The

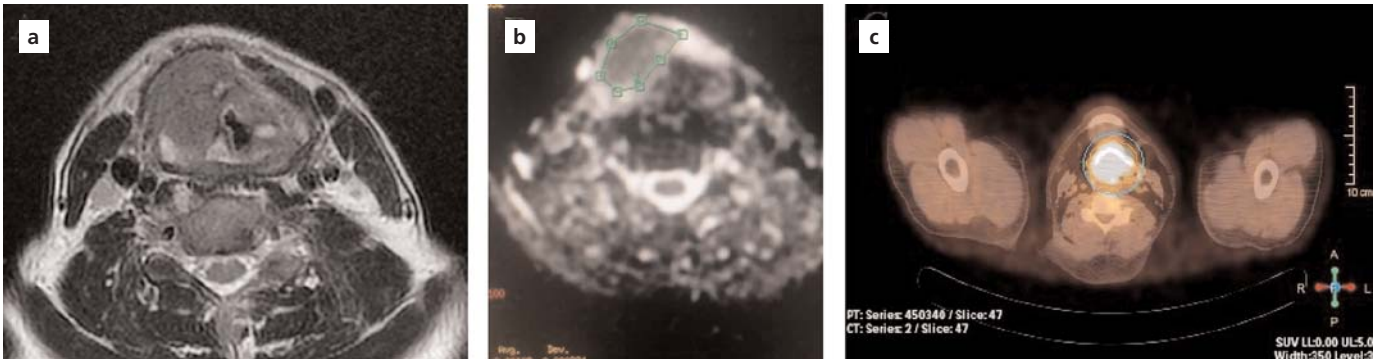


Fig. 1. Pretreatment MRI and PET/CT imaging of a case with advanced-stage laryngeal cancer. (**a**) Axial T2 weighted turbo spin echo imaging (TR/TE 4700/85), (**b**) ADC map showing laryngeal tumor with extralaryngeal extension, and (**c**) axial PET-CT demonstrated high SUV at the larynx. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

Table 1. Sociodemographic data and tumor characteristics.

Characteristics		n (%)
Sex	Female	5 (13.2)
	Male	33 (86.8)
Age	<65	13 (34.2)
	>65	25 (65.8)
Tumor location	Supraglottic	18 (47.4)
	Glottic	5 (13.2)
	Transglottic	15 (39.5)
Stage	Stage III	19 (50.0)
	Stage IV	19 (50.0)
T-stage	T3	22 (57.9)
	T4	16 (42.1)
TCI	Absent	24 (63.2)
	Present	14 (36.8)
N-stage	N0	22 (57.9)
	N1	3 (7.9)
	N2	13 (13)
LNI	Absent	22 (57.9)
	Present	16 (42.1)
PNI	Absent	30 (78.9)
	Present	8 (21.1)
Tumor differentiation	Well differentiated	3 (7.9)
	Moderately differentiated	20 (52.6)
	Poor differentiated	9 (23.7)
	Unidentified	6 (15.8)
Treatment	Surgery±Adjuvant therapy	24 (63.2)
	Radiotherapy±Chemotherapy	14 (36.8)
LRR	Absent	32 (84.2)
	Present	6 (15.8)
DM	Absent	34 (89.5)
	Present	4 (10.5)
Status	Alive	24 (63.2)
	Dead	14 (36.8)

DM: distant metastasis; **LNI:** lymph node involvement; **LRR:** locoregional recurrence; **PNI:** perinodal involvement; **TCI:** thyroid cartilage involvement

sociodemographic results and tumor characteristics are shown in **Table 1**. The median and standard deviation of pretreatment ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} values were 0.61±0.42 (range: 0.09 to 1.77) mm^2/s, 11.3±8.54 (range: 5.10 to 45.90), 12.4±10.52 (range: 3.36 to 57.79), 4.8±1.94 (range: 2.77 to 12.70), 25.8±38.33 ml (range: 1.02 to 202.24), 369.1 (range: 3.44 to 4542.10) and 132.8±277.14 (range: 2.84 to 1038.19), respectively.

Predictive value of pretreatment functional imaging-based biomarkers in patients with advanced-stage laryngeal cancer

The predictive roles of functional imaging-based biomarkers were presented in **Table 2**. Our analysis demonstrated statistically significant differences when the pretreatment SUV (stage III: 9.7±9.4 *vs.* stage IV: 11.9±7.5, p=0.02) and MTI_{mean} value (stage III: 94.4±221.0 *vs.* stage IV: 146.3±312.7, p=0.04) were compared between patients with stage III and IV. Standardized uptake value was also a predictive factor for N-stage (N0+N1: 10.4±8.5 *vs.* N2: 12.8±8.4, p=0.04). Moreover, a statistically significant difference was determined when patients with and without perinodal involvement (PNI) were compared (absent: 108.3±292.1 *vs.* present: 241.8±215.4, p=0.04).

Prognostic value of pretreatment functional imaging-based biomarkers in patients with advanced-stage laryngeal cancer

The 2-year OS, DFS and LRC were 52.6%, 57.2% and 57.2%, respectively. Log rank analysis demonstrated that none of functional imaging-based biomarkers (ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean}) had a prognostic role for oncological outcomes (**Figs. 2** and **3**).

Discussion

To the best of our knowledge, this is the first study in which various functional imaging-based biomarkers were evaluated in patients with advanced-stage laryngeal cancer using both DW-MRI and 18F-FDG PET/CT. Our literature review demonstrated that few clinical studies reported the role of both imaging techniques in head and neck cancers[15,36–41] (**Table 3**). However, the major drawback of these studies was the clinical heterogeneity of study groups in which patients with different primary tumor burdens (e.g. oropharynx, hypopharynx, nasopharynx, larynx and oral cavity) and stages were included. As a matter of fact, the measured ADC, SUV, MTV and TLG and clinical outcomes might vary significantly between abovementioned study groups. In addition, as Zhang et al. emphasized, small head and neck neoplasms are generally difficult to detect using DW-MRI; hence, the ADC values are generally unreliable.[16] Therefore, patients with early-stage laryngeal cancer were not enrolled into this study, and a homogenous group of patients with advanced-stage laryngeal cancer was particularly selected in order to determine reliable relationships between all functional imaging-based biomarkers and tumor characteristics or clinical outcomes; thereby, study group related misconceptions were minimized.

Table 2. The predictive roles of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} in advanced-stage laryngeal cancer.

		ADC		SUV		SUV_{max}		SUV_{mean}		MTV		MTI_{max}		MTI_{mean}	
		Median±SD	p	Median±SD	p	Median±SD	p	Median±SD	p	Median±SD	p	Median	p	Median±SD	p
Sex	Female	0.2±0.2	0.14	10.0±6.3	0.32	11.2±6.27	0.32	5.3±0.9	0.32	16.5±14.4	0.26	287.6	0.31	94.4±90.3	0.31
	Male	0.6±0.4		11.5±8.8		12.5±11.0		4.8±2.0		27.0±40.4		396.8		134.5±292.6	
Age	<65	0.8±0.4	0.08	10.6±7.9	0.07	11.6±10.0	0.07	4.9±1.9	0.15	27.0±27.7	0.35	229.6	0.18	94.1±208.8	0.21
	>65	0.3±0.3		11.9±8.7		12.5±10.7		4.8±1.9		25.5±43.1		371.8		134.5±308.9	
Grade	Well and moderately differentiated	0.6±0.4	0.14	12.8±9.0	0.53	13.6±11.0	0.14	5.4±1.9	0.05	32.0±45.7	0.19	453.7	0.12	148.8±319.0	0.18
	Poor	0.1±0.3		11.8±8.9		10.6±11.1		4.5±2.0		16.9±20.9		207.3		75.8±201.0	
Tumor location	Supraglottic/ Glottic	0.6±0.3	0.44	11.8±9.7	0.45	13.2±11.8	0.11	5.0±2.1	0.09	31.8±41.1	0.22	453.7	0.13	161.3±285.2	0.13
	Transglottic	0.3±0.4		11.1±6.6		10.8±8.0		4.4±1.4		24.2±34.5		247.1		94.4±269.4	
Stage	Stage III	0.3±0.3	0.14	9.7±9.4	0.02*	12.1±11.8	0.16	4.5±2.1	0.09	21.6±19.6	0.06	366.3	0.08	94.4±221.0	0.04*
	Stage IV	0.6±0.4		11.9±7.5		13.2±9.2		5.1±1.7		34.3±48.4		396.8		146.3±312.7	
T-stage	T3	0.4±0.3	0.22	10.3±10.1	0.08	12.5±12.4	0.34	4.7±2.2	0.50	22.9±20.4	0.08	369.1	0.18	106.4±232.3	0.11
	T4	0.6±0.4		11.7±5.9		11.4±7.5		5.0±1.5		35.3±51.7		373.5		141.6±322.5	
TCI	Absent	0.5±0.3	0.23	11.2±9.8	0.22	12.8±11.9	0.41	4.8±2.2	0.31	22.9±20.4	0.98	369.1	0.14	106.4±229.4	0.09
	Present	0.7±0.5		11.3±6.0		11.1±7.5		4.8±1.3		35.3±54.5		373.5		141.6±338.0	
N-stage	N0±N1	0.5±0.4	0.32	10.4±8.5	0.04*	11.6±10.7	0.15	4.5±1.9	0.11	24.2±40.6	0.31	366.3	0.24	118.4±271.0	0.21
	N2	0.6±0.3		12.8±8.4		13.6±10.4		5.3±1.9		34.3±34.8		396.8		146.3±294.6	
LNI	Absent	0.6±0.4	0.20	10.5±9.0	0.17	11.5±11.2	0.21	4.6±2.0	0.27	24.2±43.1	0.23	358.2	0.25	113.4±287.5	0.18
	Present	0.4±0.3		11.8±8.0		12.8±9.7		4.9±1.8		36.5±31.8		425.3		170.8±270.1	
PNI	Absent	0.4±0.4	0.12	10.8±8.4	0.12	11.9±10.5	0.16	4.6±1.9	0.06	23.9±41.6	0.06	300.3	0.06	108.3±292.1	0.04*
	Present	0.8±0.3		12.3±9.0		13.4±10.7		5.6±1.9		43.7±22.1		559.0		241.8±215.4	
LRR	Absent	0.5±0.4	0.09	11.3±9.1	0.47	11.9±11.3	0.46	4.8±2.0	0.47	23.9±41.3	0.16	318.9	0.24	113.3±298.9	0.21
	Present	0.9±0.4		11.2±3.3		12.8±2.8		4.9±0.9		33.1±16.9		427.0		147.5±102.8	
DM	Absent	0.6±0.4	0.33	11.1±8.0	0.25	12.3±10.0	0.43	4.8±1.8	0.34	24.8±39.7	0.11	358.2	0.19	124.7±280.7	0.14
	Present	0.5±0.4		12.6±12.7		12.0±15.3		5.0±2.7		52.6±25.3		684.5		267.0±266.1	

*Statistically significant ($p<0.05$)

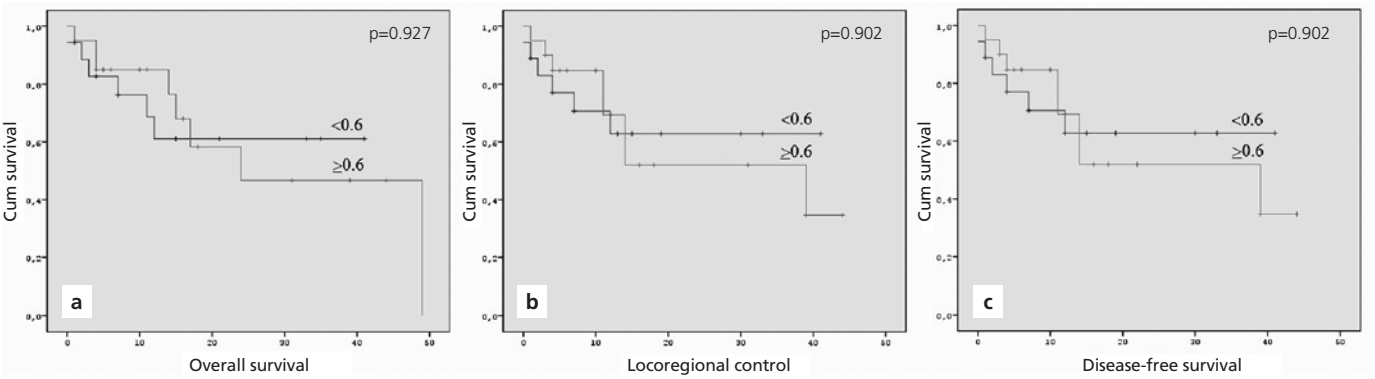


Fig. 2. The comparison of 2-year (**a**) OS, (**b**) LRC and (**c**) DFS according to pretreatment ADC values in patients with advanced-stage laryngeal cancer.

In laryngeal cancer, the association between pretreatment functional imaging-based biomarkers and tumor characteristics such as grade, neoplastic invasion or stage are inconclusive. In general, poorly differentiated tumors have more aggressive behavior and tendency to metastasize and recur. In addition, tumor cellularity is frequently high in poorly differentiated tumors. A recent meta-analysis demonstrated a moderate inverse correlation between ADC value and tumor cellularity in head and neck cancers, even though the number of included cases was less than 50 patients.[42] However, the authors emphasized that the association between ADC value and tumor cellularity var-

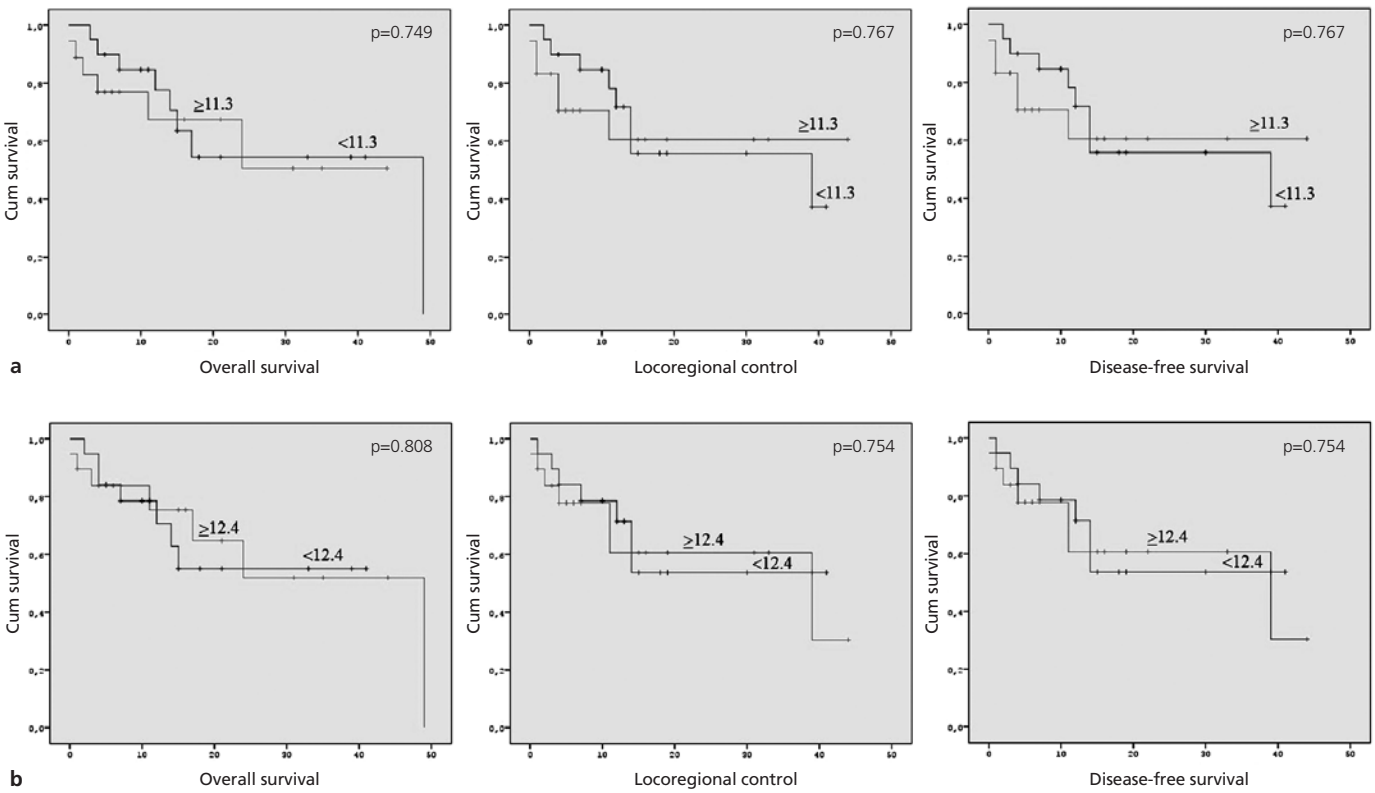
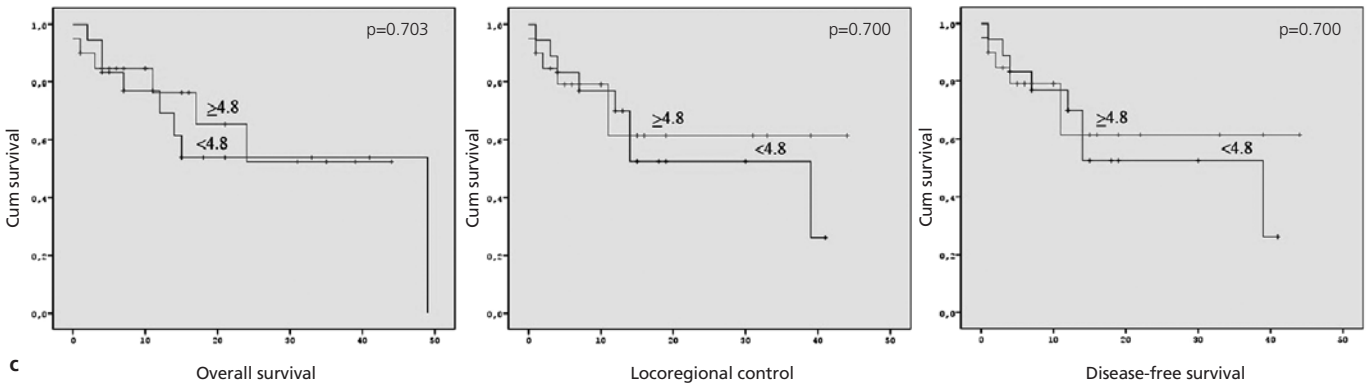
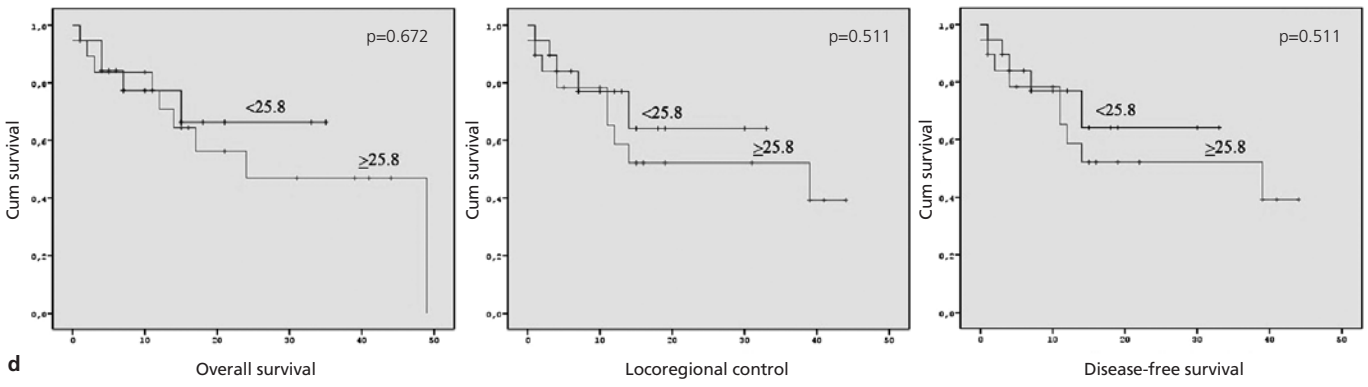


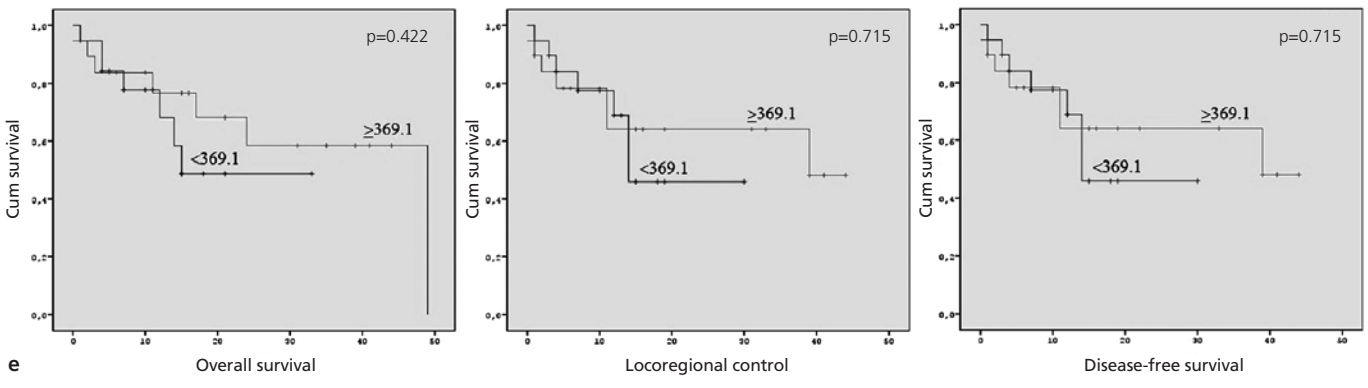
Fig. 3. The comparison of 2-year OS, LRC and DFS according to pretreatment (**a**) SUV, (**b**) SUV_{max}, (**c**) SUV_{mean}, (**d**) MTV, (**e**) MTI_{max}, and (**f**) MTI_{mean} values in patients with advanced-stage laryngeal cancer. *[Continued on next page]*


p=0.703
≥4.8
<4.8
Cum survival
Overall survival
p=0.700
≥4.8
<4.8
Cum survival
Locoregional control
p=0.700
≥4.8
<4.8
Cum survival
Disease-free survival

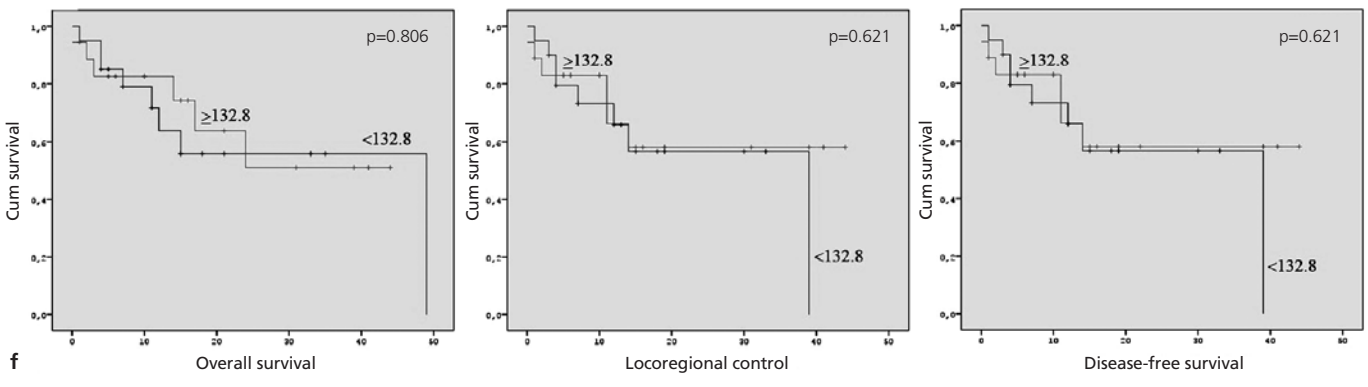
c


p=0.672
<25.8
≥25.8
Cum survival
Overall survival
p=0.511
<25.8
≥25.8
Cum survival
Locoregional control
p=0.511
<25.8
≥25.8
Cum survival
Disease-free survival

d


p=0.422
≥369.1
<369.1
Cum survival
Overall survival
p=0.715
≥369.1
<369.1
Cum survival
Locoregional control
p=0.715
≥369.1
<369.1
Cum survival
Disease-free survival

e


p=0.806
≥132.8
<132.8
Cum survival
Overall survival
p=0.621
≥132.8
<132.8
Cum survival
Locoregional control
p=0.621
≥132.8
<132.8
Cum survival
Disease-free survival

f

Table 3. Systemic review of clinical studies in which the predictive and/or prognostic roles of both DW-MRI and PET/CT were assessed in patients with head and neck cancers.

Author	Study population	Tumor location	T-Stage	N-Stage	Stage	SUV (cut-off value)	ADC (cut-off value $\times 10^{-3}$)	Treatment	Highlights
Choi et al., 2011	47	Oral cavity Pharynx Sinonasal cavity	NS	NS	NS	NA	NA	Surgery Radiotherapy Chemotherapy	Both ADC and SUV values were low in poorly differentiated tumor
Nakajo et al., 2012	26	Larynx Hypopharynx Oropharynx Oral cavity Maxillary sinus	T1–T4	N0–N3	I–IV	12.1	0.88	Radiotherapy Surgery	Lower ADC and higher SUV values were related with a significant decrease in 2-year DFS
Houweling et al., 2013	18	Oral cavity Oropharynx Nasopharynx	T1–T4	NS	NS	NS	NS	Radiotherapy	Both SUV and ADC values were helpful for dose painting in HNC
Varoquaux et al., 2013	34 (24 primary, 10 suspected recurrence)	Larynx Hypopharynx Oropharynx Oral cavity Parotid gland Paranasal sinus	T1–T4	NS	NS	NS	NS	Surgery Radiochemotherapy	There was no statistically significant relationship between tumor grade and SUV or ADC values ADCmean, ADCmin, and SUVmean values were not different between primary and recurrent HNC
Preda et al., 2016	57	Oral cavity Oropharynx	T1, T2 and T4	N0–N2	NS	5.75	ADC_{max}=1.18 ADC_{mean}=0.98 ADC_{min}=0.58	Surgery Radiochemotherapy Multimodal treatment	Patients with high SUV_{max} and ADC_{min} values had the worst prognosis

ied significantly in different types of cancers with an inconsistent data between clinical studies. They also speculated that the variability in results might be related with tumor features (cellular proliferation, nucleic areas, etc.) and microenvironment (stroma-parenchyma ratio, microvessel density, necrotic areas, etc.). In fact, Driessen et al. were unable to detect an association between ADC value and tumor grade.[43] Similarly, our results demonstrated that none of the functional based-imaging biomarkers was associated with tumor differentiation (**Table 2**). In clinical practices, the detection of neoplastic invasion of thyroid cartilage is of utmost important for treatment selection and strategy, and prognosis. Currently, CT and/or MRI are frequently used despite of inadequate sensitivity, specificity, and positive and negative predictive values.[44,45] Therefore, novel techniques are required for the improvement of these imaging modalities. Hence, Taha et al. reported that DW-MRI had high sensitivity and specificity for the prediction of TCI in patients with laryngeal cancer; however, the authors did not give any information about ADC values.[46] In addition, Kendi et al. evaluated several PET/CT-based imaging biomarkers including SUV_{max}, SUV_{mean}, SUV_{peak}, MTV, TLG, standardized added metabolic activity and normalized standardized added metabolic activity in patients with larynx cancer, and reported that none of the forementioned parameters was either sensitive or specific enough for the prediction of TCI.[47] In this study, we were also unable to detect an association between pretreatment functional imaging-based biomarkers and TCI (**Table 2**).

In fact, patients with advanced-stage head and neck cancers have a tendency to have high PET/CT-based

imaging biomarkers.[37,48] Our results also demonstrated statistically significant association between stage and pretreatment SUV (stage III: 9.7±9.4 *vs.* stage IV: 11.9±7.5, p=0.02) and MTI_{mean} (stage III: 94.4±221.0 *vs.* stage IV: 146.3±312.7, p=0.04) values. Moreover, pretreatment SUV of primary tumor were remarkably high in patients with N2-stage (N0+N1-stage=10.4±8.5 *vs.* N2=12.8±8.4, p=0.04). On the other hand, none of the functional imaging-based biomarkers demonstrated a statistically significant difference when patients with and without LNI were compared. However, pretreatment ADC value was relatively low in patients with LNI (patients without LNI: 0.6+0.4 *vs.* patients with LNI: 0.4+0.3, p=0.20). It is noteworthy that lower pretreatment ADC values were reported in metastatic cervical lymph nodes.[49–52] On the other hand, Sumi et al. detected lower pretreatment ADC values in benign lymph nodes when compared with metastatic lymph nodes.[53] Presumably, the reason for this discrepancy might be related with tumor heterogeneity and presence/absence of necrotic portions in lymph nodes.[54] Moreover, Kwee et al. emphasized the limitations in intra- and interobserver reproducibility of ADC measurements of lymph nodes.[55]

In laryngeal cancers, the prognostic role of pretreatment functional based-imaging biomarkers remains controversial. In this study, no correlation between pretreatment ADC values and oncological outcomes including 2-year OS, LRC and DFS was determined (**Fig. 2**). It is noteworthy that our literature review was unable to determine a clinical study which was particularly focused on the prognostic role of pretreatment ADC value in patients with laryngeal cancer. However, Hatakenaka et al. examined the prognostic role of pretreatment ADC values in patients treated with radiotherapy for head and neck cancers and determined high risk of local failure in patients with high pretreatment ADC value.[56] Similarly, Preda et al. emphasized that high pretreatment ADC_{min} value (cut-off value: 0.58×10^{-3} mm^2/s) was a poor prognostic factor for patients with head and neck cancer.[40] In contrast, Nakajo et al. reported a significant decrease in 2-year DFS in patients with low pretreatment ADC value (cut-off value: 0.88×10 mm^2/s).[37] Nevertheless, both Preda et al. (cut-off value: 5.75) and Nakajo et al. (cut-off value: 12.1) demonstrated an inverse correlation between pretreatment SUV of primary tumor and survival in patients with head and neck cancers. However, Park et al. were unable to determine a statistically significant correlation between pretreatment SUV_{max} (cut-off value: 10) and oncological outcomes including 3-year LRC and OS in patients with laryngeal and hypopharyngeal cancer.[57] On the other hand, Kitajima et al. particularly evaluated the prognostic value of pretreatment SUV in patients with laryngeal cancer and reported that pretreatment SUV of primary tumor (cut-off value: 2.85) was a prognostic imaging biomarker for patients who were treated by radio±chemotherapy.[58] Interestingly, they did not find a correlation between pretreatment SUV of primary tumor (cut-off value: 8.6) and survival in patients who were treated by surgery with/without adjuvant treatment. In contrast, Joo et al. reported that patients who were treated by supracricoid laryngectomy had unfavorable outcome and poor prognosis when the pretreatment SUV_{max} of primary tumor was higher than 7.0.[59] In our study, we were unable to determine a correlation between pretreatment SUV (cut-off value: 11.3), SUV_{max} (cut-off value: 12.4), and SUV_{mean} (cut-off value: 4.8) of primary tumor and oncological outcomes (**Fig. 3**). It is known that patient related- (e.g. plasma glucose level, body mass index, etc.), tumor related- (e.g. tumor size, shape and microenvironment) and technique related-factors (e.g. post-injection PET scan time, acquisition protocol, imaging procedure, software, etc.) may affect the measured SUV values. Therefore, a variety of novel quantification techniques such as MTV and TLG were presented recently. A systematic review and meta-analysis demonstrated that MTV and TLG were prognostic imaging biomarkers for patients with head and neck cancers, and high MTV and TLG values caused more than 3-fold increase in mortality risk.[60] However, the authors also noted that their study had several limitations including different cut-off values for MTV and TLG, protocol related measurement changes, and clinical heterogeneity (e.g. primary tumor burden, tumor differentiation and stage) in head and neck cancers. Nonetheless, Yabuki et al. determined an inverse correlation between pretreatment MTV values (cut-off value: 4.9 ml) and survival in patients who were treated by radio+chemotherapy for laryngeal cancer.[61] Furthermore, same group also reported that patients with high pretreatment MTV values (cut-off value: 4.9 ml) had better survival outcomes when surgery-based treatment strategy was performed.[62] Hence, they suggested that MTV might be used for treatment selection in laryngeal cancer. As abovementioned, our study population was composed of patients with advanced-stage laryngeal cancer; therefore, the median value for MTV (cut-off value: 25.8 ml) was remarkably higher than forementioned studies. However, our results did not show a survival difference between patients with high and low MTV values (**Fig. 3**).

Conclusions

This is the first study that particularly focused on evaluating the predictive and prognostic roles of pretreatment functional imaging-based biomarkers in patients with advanced-stage laryngeal cancer. Our results obviously demonstrated that pretreatment SUV and MTI_{mean} values were predictive factors for staging, N-stage and PNI. Indeed, functional imaging-based biomarkers are promising, novel, non-invasive techniques that may provide additional information about tumor characteristics, treatment selection and prognosis in the near future. However, tumor- and protocol related differences are the major drawbacks. Therefore, well-stratified, multicenter, prospective clinical studies with tumor-specific standardized cut-off values and protocols are required.

Conflict of Interest: No conflicts declared.

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