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Evaluation of the prognostic value of 18F-FDG-PET/CT parameters in head and neck cancer patients treated with definitive intensity modulated radiotherapy

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Abstract

Purpose

To investigate the treatment outcome and prognostic factor of volumetric parameters measured by 18F-FDG-PET/CT in squamous cell carcinoma patients of oropharynx, hypopharynx, and larynx treated with definitive intensity modulated radiotherapy.

Methods

We retrospectively reviewed 63 patients who received definitive radiation therapy for head and neck squamous cell carcinoma (HNSCC) between April 2007 and March 2012 in our hospital. Clinical factor and 18F-FDG-PET/CT parameters were evaluated using univariate and multivariate Cox regression analysis.

Result

With a median follow up of 61months (range 4-116 month), the 5-year overall survival (OS), progression-free survival (PFS) rate was 58.2%, and 63.0%, respectively. Recurrence was observed in 24 patients. Seventeen patients had locoregional recurrence and 9 patients developed distant metastasis. ROC analysis revealed the best threshold of pretreatment FDG-PET parameters was 14.8 of SUVmax, 5.4ml of metabolic tumor volume (MTV), and 38.5ml of total lesion glycolysis (TLG). On univariate analysis, MTV (>5.4ml), and TLG (>38.5ml) were predictive of poor OS ($p<0.01$, $p<0.01$) and poor DFS ($p=0.01$, $p<0.01$). On multivariate analysis, MTV displayed significantly worse effects on OS and DFS ($p= 0.02$, <0.01, respectively), while SUVmax was nonsignificant ($p=0.70$ for OS, $p=0.70$ for DFS).

Conclusion

This study showed that18F-FDG-PET/CT parameters are useful as prognostic factor of definitive intensity modulated radiotherapy of HNSCC. These prognostic factors may identify the population who have benefit from high intensity treatment, ex. dose escalation planning.

Introduction

Radiation therapy is one of principal treatments for head-and neck carcinoma (HNC). Definitive chemoradiotherapy in patients with advanced HNC can preserve laryngopharyngeal function such as speaking, swallowing, and breathing. Radiotherapy of head-and-neck cancers needs to minimize radiation exposure to a large number of organs-at-risk (OARs). Intensity modulated radiotherapy (IMRT) can reduce complication and escalate dose prescription [1]. Improvements in identification of the tumor volume of head and neck tumors using imaging such as ^{18}F labeled Fludeoxyglucose positron emission

tomography with computed tomography (18F-FDG-PET/CT) have facilitated radiation treatment planning by improved target volume delineation and more accurate target localization, which is critical for IMRT planning. Sharp dose gradients between the high dose region targeted at the tumor and adjacent low dose normal tissue regions in IMRT improved the therapeutic ratio between tumor control and radiation related toxicity, although this is reliant on the accurate identification of the tumor extent.

18F-FDG-PET/CT is a medical imaging technique based on the study of glucidic metabolism of tumor cells [2]. During the last decade, it has emerged as an essential imaging tool in the field of oncology, not only for diagnosis but also for prognostic and therapeutic evaluation [3,4]. Concerning HNSCC disease, there have been many studies investigating the prognostic value 18F-FDG-PET/CT. In fact, the maximum standardized uptake value (SUVmax), a semi-quantitative measure of tumoral uptake, is a predictor of survival, regardless of the size and stage of the tumor but without a real cut-off set, varying between 4 and 10 according to previous studies [5,6]. On the other hand, metabolic tumor volume (MTV) defined as the volume of FDG activity in a tumor assessed by automated volume of interest (VOI) delineation has been proposed as a quantitative PET index. MTV has been reported as an additional diagnostic [7] and prognostic imaging biomarker in various solid cancers [8]. A large MTV has been already suggested as a poor prognostic factor in HNSCC, and even seems a better predictor of survival than SUVmax [9].

The relative importance between SUV, MTV, and total lesion glycolysis (TLG) of the primary tumor in the risk stratification of HNSCC patients has not been determined. In our study, we analyze recurrence predictor using 18F-FDG-PET/CT parameters in head and neck squamous cell carcinoma treated with definitive IMRT and try to determine which population needs dose escalation or dose painting.

Materials And Methods

Patients

Retrospectively, we analyzed consecutive 63 patients with histologically proven oropharyngeal and hypopharyngeal squamous cell carcinoma. They underwent definitive IMRT in our institution from April 2007 to March 2011. All patients had 18F-FDG PET/CT image data from multi-institution when we planned IMRT.

The primary sites were the oropharynx in 16 patients, and hypopharynx in 37. The median patient age was 61 years (range 40–91 years) and the 48 patients are male. The patients' characteristics are shown in Table I. The patients were staged according to the malignant tumour criteria of the Union for International Cancer Control (6th edition) [10]. The clinical stage was I, II, III, IVA, and IVB in 5, 8, 4, 33, and 3 patients, respectively. Written informed consent was obtained from all patients and the study was approved by the local ethics committee.

Treatment

Definitive radiotherapy was carried out using standard dose fractions. All patients were treated with photon beam. Simultaneous integrated boost (SIB)-IMRT was used in all cases. The prescription dose was 70Gy in 2Gy fractions for primary tumor and positive lymph node, and 63Gy in 1.8Gy fractions for high-risk clinical target volume (CTV), and 56Gy in 1.6Gy fractions for low-risk CTV.

Twenty-one patients received neoadjuvant chemotherapy and 48 patients received concurrent chemotherapy, and 10 patients received neck dissections before radiotherapy.

PET/CT parameters

All patients underwent the initial PET/CT before treatment. Because patients received PET/CT at multicenter institutions, the study protocol is uncertain in detail. To revise the multicenter value, we calculate TBR in addition to SUVmax. The PET images were displayed on a workstation (MIM maestro, version 6.5.3). We used auto-contouring program by thresholds.

Statistical Analysis

Statistical analyses were performed using EZR ver. 1.31 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria) [11]. We examined the association between patient outcome and PET/CT parameters using the univariate Cox proportional hazards regression analysis.

For assessment of patient outcome, we calculated overall survival (OS), disease-free survival (DFS), and loco-regional control (LRC) rates, and distance control (DC) rate. Outcomes were calculated as the time between the start of radiotherapy and the event or the last clinical follow-up.

Result

The median follow-up period was 61 months (range, 4-116 months) . In total, 24 patients had disease recurrence and 26 patients died during follow-up. The median OS and DFS were 77.2 month [95% confidence interval (CI): 40.4-NA] and 105.7 months [95% CI: 19.6-NA], respectively. The 5-year OS and PFS were 58.2% and 63.0%, respectively. Patient characteristics are shown in Table 1. Details of the neoadjuvant and concurrent chemotherapy and neck dissections are also described.

FDG PET/CT findings and Patient Outcome

The thresholds of each parameter were determined according to the ROC analysis results, and optimal cutoffs of 14.8, 8.7, 5.4 ml and 38.5 ml were chosen for SUVmax, TBR, MTV, and TLG, respectively. We performed subgroup analysis using the Kaplan-Meier method and log-rank tests to evaluate the differences between groups, and MTV and TLG were found to be significant predictors of OS, DFS, LRC, and DC (MTV; p=0.002, <0.001, 0.025, and 0.008, respectively, TLG; p=0.013, 0.005, 0.029, and 0.104, respectively) as shown in Figure 1, and Table 2.

Recurrence pattern and localization of local failure

At the time of data cut-off (28 May 2017), PFS events were observed in 24 patients and 30 patients had dead. The local recurrence was occurred in 10 patients. As for local recurrence, MTV and TLG were significant predictors (all, $p<0.01$) (Figure 2). In 5 of the 10 patients whose 18F-FDG-PET were available, the recurrence tumor volume was included in initial clinical target volume, and the distance between the two points of the SUVmax of initial target volume and recurrence volume was mean 1.4±SD0.5cm. Representative images from patients are shown in Figure 3.

Discussion

This study showed that MTV and TLG are superior prognostic biomarkers of treatment outcome and survival for HNSCC patients undergoing definitive IMRT as compared to SUVmax or TBR. MTV will be useful to identify a subgroup of patients with a poor diagnosis who may benefit from aggressive therapy such as dose escalation aiming to improve their survival.

Schwartz et al. [12] evaluated 54 patients with HNSCC, undergoing RT including postoperative patients with or without concurrent chemotherapy, and reported that a SUV of greater than 9, the median, significantly correlated with inferior local control and disease-free survival. On univariate and multivariate analyses these data remained significant or borderline significant. Similarly, Machtay et al. [13] reported in a cohort of 60 HNSCC patients, treated with definitive radiotherapy with or without concurrent chemotherapy, that an SUVmax<9, median SUVmax of the study was 7.2, was associated with improved 2-year DFS of 72 versus 37% ($p = 0.007$). Torizuka et al. [14] reported in 50 consecutive HNSCC patients who underwent definitive RT with or without chemotherapy, or surgery with or without postoperative RT that an SUVmax of B7 significantly predicted higher rates of 2-year local control and disease-free survival. When adjusted for age and nodal stage these findings remained significant. However, the median SUVmax for the cohort was 10.53, and they did not identify how an SUV max of 7 was selected as the optimal cut point. Limitations of comparing SUV as a radiological biomarker between studies includes the use of different SUV cutoff values which may be influenced by multiple factors including patient selection, differences in imaging technique, injected FDG dose, incubation period, protocol, scanner, and reconstruction algorithm variation [15–17].

As time passed by, MTV and TLG was defined in 2009 and 2011, respectively [18, 19]. MTV is defined as the volume of the tumor demonstrating FDG uptake. It represents a volumetric and metabolic biomarker, and estimates tumor volume based on the distribution of metabolic activity. Therefore, unlike SUVmax, which is a single-pixel representation of the maximum FDG uptake by the tumor, MTV quantifies the overall tumor burden [20]. Thus, volume-based parameters, such as MTV, were sought in hopes of identifying more accurate ways to prognosticate disease. TLG is defined as the tumor volume multiplied by SUVmean of included voxels. Because this parameter incorporates both the MTV and SUV, it represents both the degree of FDG uptake and the size of the tumor. Like MTV, TLG theoretically

represents the total activity of the metabolically active cancer cells. It should be an ideal representation of overall tumor burden. La et al. [21] found that only tumor volume as measured on PET, not the SUV, was associated with progression free survival and overall survival in patients with head and neck cancer. These results are similar to our findings that the MTV was a more accurate predictor than the SUVmax with regard to response to treatment and the progression free survival. The significance of being able to stratify patients according to their MTV at diagnosis into two distinct outcome groups suggests that its specific value is significant, and that the MTV might be a quantitative biomarker for predicting which patients will have a worse outcome before treatment is initiated.

This study had some limitations. First, because this was a retrospective study in a single institute, information bias was inevitable, and sample size was small. The heterogeneity of the primary tumor site, the high population of advanced stage, and the nonuniform the treatment regimens. Second, the human papilloma virus (HPV) status of the oropharyngeal lesions was not determined, because at the start of this study HPV/p16 status was not examined routinely in our institution. Despite these limitations, we obtained significant results indicating that MTV and TLG was an important prognostic factor in patients with HNSCC.

Recently, in addition to these general features such as SUVmax, MTV, and TLG, textural feature analysis as part of radiomics is an emerging field in quantitative medical imaging analysis, allowing to extract higher dimensional features from grey level distribution of image that are unrecognizable by visual inspection as a further approach.

Conclusion

This study showed that MTV and TLG are superior prognostic utility of treatment outcome and survival for HNSCC patients undergoing definitive IMRT as compared to SUVmax or TBR. MTV will be useful to identify a subgroup of patients with a poor diagnosis who may benefit from aggressive therapy such as dose escalation aiming to improve their survival.

Declarations

Acknowledgements

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Conflict of Interest

We have no financial relationships to disclose.

Ethical statement:

This study was approved by the local ethical committee of Kyoto University Hospital.

Presentation: Presented at the 2017 annual meeting of the Japan Society of Clinical Oncology, Yokohama, Japan.

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Tables

Table 1. Patients` characteristics

Age (years)	40-91	(median 61)
Gender		
Male	54	(85.7 %)
Female	9	(14.3 %)
Histology		
Squamous cell carcinoma	61	(96.8 %)
Undifferentiated carcinoma	2	(3.2 %)
Tumor location		
Oropharynx	23	(36.5 %)
Hypopharynx	39	(61.9 %)
Larynx	1	(1.6 %)
Stage (6th ed.)		
I	5	(7.9 %)
II	7	(11.1 %)
III	8	(12.7 %)
IV	43	(68.3 %)
Total dose of radiotherapy (Gy)	70	
Chemotherapy regimen.		
CDDP or CBDCA	51	(81.0 %)
Other	2	(3.2 %)
RT alone	10	(15.9 %)
Neoadjuvant chemotherapy		
FP	14	(22.2%)
TPF	14	(22.2 %)
Neck Dissection	7	(11.1 %)

Abbreviations: CDDP=cisplatin, CBDCA=carboplatin, FP=cisplatin+5-FU, TPF=docetaxel+ cisplatin+5-FU

Table 2 PET/CT parameters, and survival and disease control status

		Locoregional control	Distant control	Overall survival	Disease-free survival
Median	**n**	**Events (5-year actuarial control rates)**			
All	63	72.7 %	82.0 %	58.2 %	63.0 %
SUVmax					
< 14.8	45	74.3 %	85.3 %	64.4 %	68.5 %
> 14.8	18	68.4 %	73.1 %	41.9 %	50.0 %
p value		0.643	0.381	0.071	0.171
TBR					
< 8.7	44	75.8 %	86.6 %	61.3 %	67.7 %
> 8.7	19	65.6 %	71.5 %	50.5 %	52.6 %
p value		0.233	0.164	0.397	0.158
MTV					
< 5.4 ml	49	78.7 %	88.7 %	66.7 %	73.1 %
> 5.4 ml	14	43.2 %	60.6 %	28.6 %	28.6 %
p value		0.025	0.008	0.002	<0.001
TLG					
< 38.5 ml	43	80.4 %	87.5 %	67.4 %	74.0 %
> 38.5 ml	20	55.5 %	67.6 %	37.7 %	40.0 %
p value		0.029	0.104	0.013	0.005

Figures

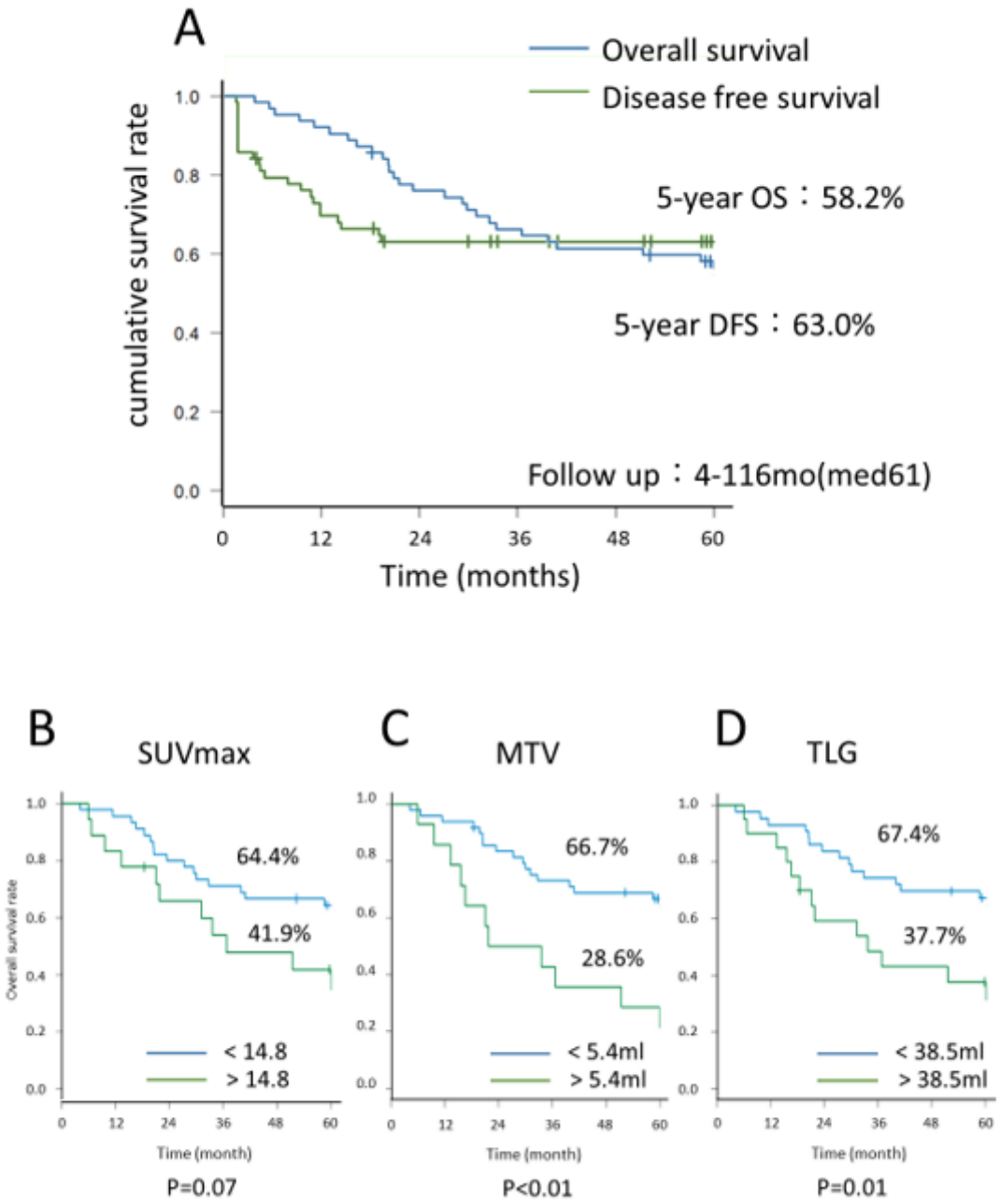

Figure 1

Overall survival according to PET/CT parameters.

A-D, Kaplan Meier survival curves with all patients (A), and between groups for maximum standardized uptake value (SUVmax) (B), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) (D).

Figure 2

Local recurrence according to PET/CT parameters

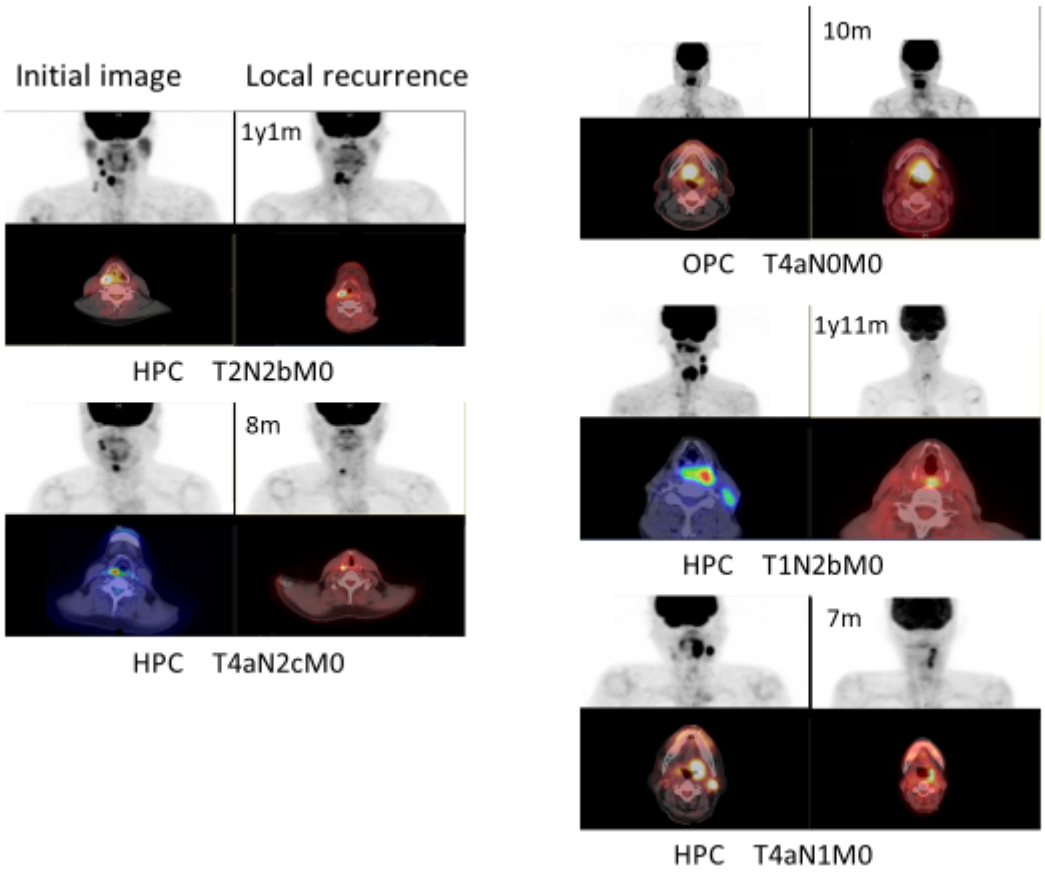

Figure 3

Representative images of patients with local recurrence after definitive IMRT.