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ORIGINAL ARTICLE

Predictive markers, including total lesion glycolysis, for the response of lymph node(s) metastasis from head and neck squamous cell carcinoma treated by chemoradiotherapy

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Abstract
Background Chemoradiotherapy (CRT) is used to treat cervical lymph node(s) metastatic head and neck cancer patients. Evaluation and treatment of lymph node(s) after CRT is important to improve the prognosis.
Methods Prior to CRT, we determined the TNM stage by visual and imaging examinations. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were calculated from the results of fluorodeoxyglucose-positron emission tomography (FDG-PET). After CRT, the patients were divided in two groups—complete response (CR) and non-CR—and their responses were compared with the clinical characteristics.
Results T4, N2b, N2c and $TLG_{2.5} \geq 18.8$ were statistically significant predictive indices before CRT. The odds ratio, 95 % confidence interval and *p* value were, respectively—T4: 2.73, 1.15–6.51, 0.0230; N2b: 6.96, 1.50–32.3, 0.0132; N2c: 11.80, 2.37–58.50, 0.00258; and $TLG_{2.5} \geq 18.8$: 6.25, 2.17–18.00, 0.000672.
Conclusions TLG was found to be a good predictive factor for metastatic lymph node(s) prior to CRT treatment. After CRT treatment, FDG-PET was found to be highly specific and useful for negative screening.

Keywords Head and neck squamous cell carcinoma · Metastatic lymph node · Chemoradiotherapy · Total lesion glycolysis · Predictive factor

Introduction

The definitive treatment for locoregionally advanced head and neck squamous cell carcinoma (HNSCC) is radiotherapy and/or surgical resection. Due to the anatomical features of the head and neck, organ preservation is important to maintain functions and to minimize aesthetic changes. To preserve function, some authors have described the efficacy of chemoradiotherapy (CRT) and neo-adjuvant (induction) chemotherapy followed by definitive radiotherapy for advanced HNSCC patients [1–11]. Until recently, planned neck dissection (PND) after CRT was a common treatment method for lymph node(s) metastatic advanced HNSCC. However, improvements in chemotherapy regimens and in the accuracy of radiotherapy and diagnostic imaging systems have resulted in improved treatment results and accuracy of metastatic lymph node(s) evaluation. Therefore, early salvage neck dissection has recently become the standard therapy for neck lymph node(s) failure after CRT [12]. To better predict the necessity of neck dissection after CRT, we evaluated pre-treatment clinical factors, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) calculated from fluorodeoxyglucose-positron emission tomography (FDG-PET) results, as failure risk factors in comparison with clinical results.

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Patients and methods

Study design

This was a retrospective study. Institutional review board approval was obtained prior to data collection.

Patients

Since January 2002, FDG-PET/PET-computed tomography (CT) has been performed for head and neck carcinoma patients in our institute. Eligibility criteria for our study included written informed consent from the patient, the presence of an untreated lymph node-positive squamous cell carcinoma in the head and neck region, a TN classification determined according to the 2009 staging system of the UICC (7th edition), the availability of pre- and post-CRT results for contrast-enhanced CT and/or gadolinium (Gd)-enhanced magnetic resonance imaging (MRI), ultrasound, and FDG-PET/PET-CT, to allow clinical evaluation of the treatment response by follow-up of at least 6 months duration from the end of CRT or confirmation of death within 6 months after the end of therapy.

Treatment

Radiotherapy was delivered in conventional fractions of 1.8 Gy to a total dose of 66.6–70.2 Gy, 5 days per week, using 4–6 MV X-rays. The radiation fields were set up as follows—the primary tumor, and prophylactically, the bilateral cervical lymph node area (levels I–V and retropharyngeal lymph node area) for the nasopharynx, oropharynx, hypopharynx, larynx, oral cavity, and primary unknown carcinoma; the primary tumor, and prophylactically, the bilateral cervical lymph node area (levels I–V area) for two maxillary sinus carcinomas (one N2b and one N2c) and one ethmoid carcinoma; the primary tumor, and prophylactically, the ipsilateral cervical lymph node area (levels I–V area) for one maxillary sinus carcinoma (N1). Lateral-opposed fields to the upper neck and an anterior field to the lower neck were used. The cervical lymph node area received prophylactic doses of 45 Gy. The CRT regimens were decided on the basis of age and/or comorbidity according to our previous reports [4–11]. The chemotherapy regimens were as follows—the PFML regimen [7, 8, 11] consisted of cisplatin (60 mg/m^2, day four), 5-fluorouracil (600 mg/m^2, days one−five), methotrexate (30 mg/m^2, day one), and leucovorin (20 mg/m^2, days one−five); the TPF regimen [5, 11] consisted of docetaxel (50 mg/m^2, day one), cisplatin (60 mg/m^2, day four), and 5-fluorouracil (600 mg/m^2, days one−five); the S-1 regimen [10] consisted of the oral administration of S-1 with the dose adjusted according to the body surface area; the CBDCA and UFT regimen [4, 9] consisted of carboplatin (area under the curve [AUC] = 5, once per week) and UFT (300 mg/day, everyday); and the TXT regimen [6] consisted of an intravenous infusion of docetaxel (10 mg/m^2) once a week. The PFML and TPF regimens were administrated as anti-tumor chemotherapy for healthy young patients, and the CBDCA and UFT, S-1 and TXT regimens were used as radiosensitizing chemotherapy for elderly and/or complicated patients.

FDG-PET/PET-CT measurements

The standard uptake value (SUV) was defined as the radioactive concentration in the tissue (becquerels per gram) divided by the injected dose (becquerels) divided by the patient's body weight [grams]. The metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured and calculated at the pre-treatment evaluation using Synapse Vincent software (Fujifilm, Tokyo, Japan) for volumetric analysis based on FDG-PET or PET-CT results. FDG-PET data were transferred into the workstation in DICOM format and intensity values were automatically converted to SUVs. For MTV calculations, the contour margins around the neck lymph node(s) were set at SUV = 2.0, 2.5, 3.0, 3.5 and 4.0. Using a graphical user interface, we drew a region of interest that enclosed the whole hypermetabolic neck lymph node(s) lesion on each axial, coronal and sagittal slice. The tumor volume was then delineated for each SUV iso-contour. The software automatically calculated the volume of neck lymph node(s) within each region of interest. TLG values were calculated by multiplying each MTV by the SUV_{mean}.

Clinical evaluation

A clinical complete response (CR) was defined as the absence of recurrence together with pathological CR in neck-dissected patients, and a determination of clinical non-CR was defined as the presence of remnant tissue together with pathological evaluation in neck-dissected patients.

The recurrence of lymph node metastasis (once evaluated as CR) was defined as either an obvious increase in size by manual and imaging examinations, or an elevation in SUV value according to FDG-PET/PET-CT, and/or positive fine-needle aspiration cytology results at ≥6 months after the end of CRT. Cases showing re-growth of the lymph node(s) within 6 months after CRT were defined as remnant tumors (non-CR).

Statistical analysis

Statistical analysis was performed using EZR software [13]. Univariate analysis was performed using Fisher's exact

test to examine relationships between clinical response and pre-treatment evaluations, i.e., age (≥64 or <64, the median age), sex, chemotherapy (PFML and TPF regimens were considered as anti-tumor chemotherapy, while S-1, CBDCA and UFT, and TXT regimens were considered as radiosensitizing chemotherapy), primary site, TN stage, $MTV_{2.5}$, $TLG_{2.5}$. Multivariate logistic regression analysis was performed to examine the relationship between clinical response and the results of univariate analysis.

Results

Patients

A total of 235 patients were enrolled. Patient characteristics are summarized in Table 1. Of these patients, seven had insufficient imaging evaluation, six were confirmed to have remnant tissue at the primary site and refused to have definitive surgery, two dropped out, one did not receive concurrent chemotherapy during radiotherapy, and one died from ileus at 4 months after CRT. Therefore, 218 patients were analyzed in this study.

Clinical evaluation

A clinical CR in the neck was obtained in 189 cases (86.7 %) and non-CR in 29 cases (13.3 %).

MTV and TLG

To determine the SUV cut-off value, MTV and TLG were measured and calculated at SUVs of 2.0, 2.5, 3.0, 3.5 and 4.0 in all patients. The receiver operating characteristic (ROC) curves were confirmed between these results and the clinical response. An SUV cut-off value of 2.5 showed the largest AUC for both MTV and TLG; the cut-off value for $MTV_{2.5}$ was determined to be 5.2 and the cut-off value for $TLG_{2.5}$ was determined to be 18.8 by ROC (Fig. 1).

Univariate and multivariate analysis

Univariate analysis (Table 2) revealed the significant predictive factors ($p < 0.05$) for clinical evaluation to be a primary site in the nasopharynx or hypopharynx, a T stage of T4, an N stage of N1 or N2c, and $MTV_{2.5}$ and $TLG_{2.5}$. Multivariate logistic regression analysis (Table 3) was performed to examine the relationships between clinical response and the results of univariate analysis for those factors with a p value <0.15, i.e., sex, chemotherapy, a primary site in the nasopharynx, hypopharynx or larynx, a T stage of T1, T2 or T4, an N stage of N1, N2b or N2c, and $MTV_{2.5}$ ≥5.2, and $TLG_{2.5}$ ≥18.8. Results revealed that T4 (odds ratio 2.73, 95 % CI 1.15–6.51, $p = 0.0230$), N2b (odds ratio 6.96, 95 % CI 1.50–32.3, $p = 0.0132$), N2c (odds ratio 11.80, 95 % CI 1.37–58.50, $p = 0.00258$), and $TLG_{2.5}$ ≥18.8 (odds

Table 1 Patient characteristics

Age (years)	
Range	16–92
Median	64
Gender (*n*)	
Male	197
Female	38
Primary site (*n*)	
Nasopharynx (NPC)	26
Oropharynx (OPC)	73*
Hypopharynx (HPC)	89*
Larynx	29*
Oral cavity	11*
Nasal/para-nasal	4
Unknown primary	9
*OPC + HPC	4
*OPC + larynx	1
*Larynx + oral cavity	1
T classification (*n*)	
T1	20*
T2	86*
T3	44*
T4	82*
Tx	9
*T1 + T3	1
*T1 + T4	1
*T2 + T3	2
*T2 + T4	1
*T3 + T4	1
N classification (*n*)	
N1	53
N2*	166
N3	16
*N2 (NPC)	13
*N2a	8
*N2b	96
*N2c	49
Radiation dose (*n*)	
61.2–64.8 Gy	4
66.6–70.2 Gy	228
72.0–75.6 Gy	3
Chemotherapy (*n*)	
Antitumor chemotherapy	151
Radiosensitizing chemotherapy	83
None	1

TPF, PFML, CBDCA + UFT, TXT and S-1 represent the chemotherapy regimens described in ('patients and methods')

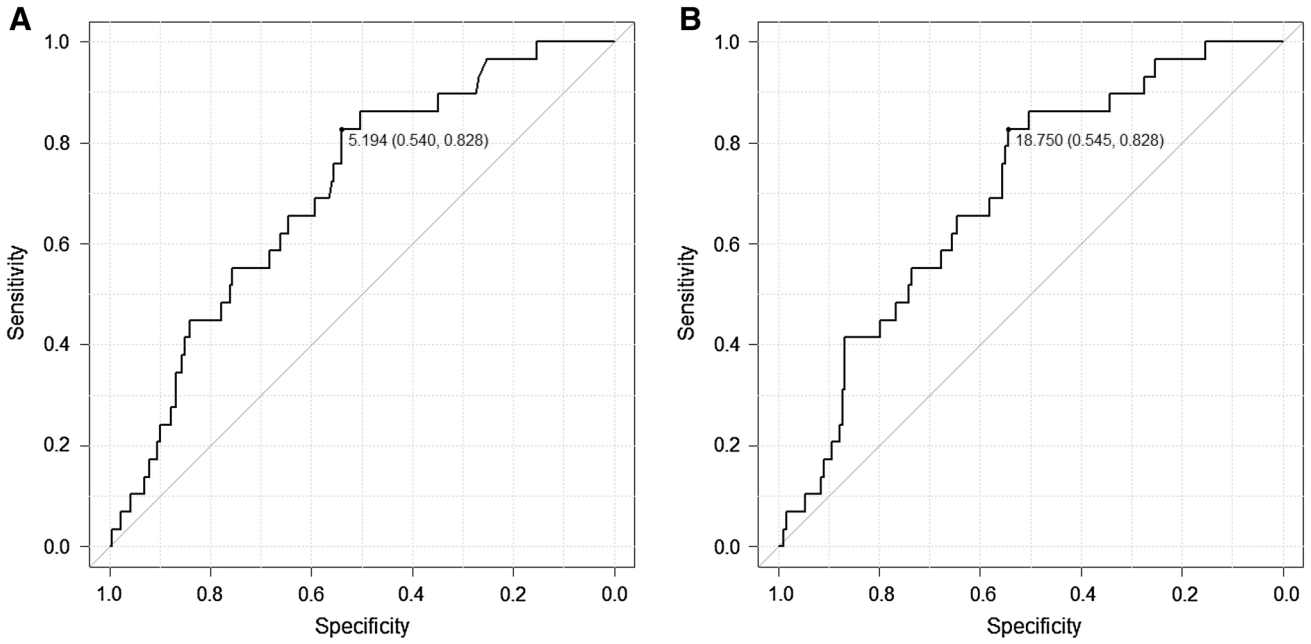

Fig. 1 ROC using **a** $MTV_{2.5}$ and **b** $TLG_{2.5}$ to predict the clinical course of neck lymph node metastasis. *ROC* receiver operating characteristic curve, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

ratio 6.25, 95 % CI 2.17–18.00, $p = 0.000672$) were significant predictive factors prior to CRT.

Patient outcome

In the 189 clinical CR cases, the follow-up period ranged from 6−167 months (median 46 months). In this group, 46 patients had locoregional recurrence and/or distant metastases. The types of relapse included primary site recurrence ($n = 13$), neck lymph node(s) recurrence ($n = 13$), distant metastasis ($n = 11$), primary and neck lymph node(s) recurrence ($n = 5$; Fig. 2), primary recurrence and distant metastasis ($n = 1$), and neck lymph node(s) recurrence and distant metastasis ($n = 3$). Of these patients, seven underwent definitive surgery (neck dissection [$n = 6$], primary resection [$n = 2$]; and both primary resection and neck dissection [$n = 1$]), and three (nasopharyngeal carcinoma patients with recurrence confirmed only in the primary site) received additional radiotherapy. Thirty-eight patients indicated cause-specific death and eight patients were alive (seven patients were alive with tumor-free status and one with tumor-dormant status). Seventeen patients died of non-specific causes.

In the clinical non-CR 29 cases, the follow-up period ranged from 3−84 months (median 13 months). In this group, 12 patients underwent neck dissection with or without primary site resection, and 17 refused additional treatment and received best supportive care. Of the 12 operated cases, six died of disease-specific causes, five were alive with a tumor-free status, and one with a tumor-dormant status.

Discussion

The cure of metastatic lymph node(s) is a prognostic factor for advanced HNSCC. With recent advances in CRT, i.e., improvements in chemotherapy regimens, radiotherapy techniques, and the effective handling of adverse events, the treatment results for metastatic neck lymph node(s) after CRT have been improving. In cases with apparent remnant lymph node(s) after CRT, neck dissection is performed as the definitive therapy; however, the indication of neck dissection followed by CRT in cases with a CR has also been discussed. In the early days of CRT treatment, PND was performed after definitive radiotherapy for patients who were suspected of having a remnant tumor, particularly in patients with N2 or N3 disease [14, 15]. Recently, PND is considered to be an unacceptable treatment [12, 16] due to the rate of isolated neck failure, i.e., recurrence only in the neck lymph node(s) but not in the primary site after both sites have been evaluated as CR after CRT is reported to be 0–5 % [17–19]. Recurrence can be detected in the early period of neck lymph node relapse by FDG-PET/PET-CT [20]. The control of metastatic neck lymph node(s) by CRT and early salvage neck dissection require a highly accurate evaluation system, which can be obtained by a combination of methods with high sensitivity and high specificity. We propose that FDG-PET/PET-CT is useful as a highly specific screening test for CR evaluation, and ultrasonography is useful as a highly sensitive screening test for non-CR evaluation of metastatic lymph node(s) response after CRT [21].

Table 2 Results of univariate analysis between clinical evaluation and pre-treatment indexes

Prognostic factors	Clinical (*n*)	Non-CR (*n*)	*p* value
Age (years)			
<64	94	15	1.00
≥64	95	14	
Sex			
Male	156	27	0.122
Female	33	2	
Chemotherapy			
Anti-tumor	130	15	0.0613
Radiosensitizer	59	14	
Primary site			
Nasopharynx (NPC)	23	1	0.0514
Oropharynx	59	9	0.831
Hypopharynx	69	15	0.0141
Larynx	25	0	0.0514
Oral cavity	9	2	0.645
Nasal/para-nasal	1	2	0.352
Unknown primary	8	1	1.00
TN stage			
T1	15	1	0.138
T2	7	9	0.107
T3	38	3	0.614
T4	58	16	0.00157
N1	49	2	0.000293
N2 (NPC)	13	0	0.225
N2a	6	1	1.00
N2b	70	17	0.112
N2c	36	8	0.0136
N3	15	1	1.00
$MTV_{2.5}$			
<5.2	103	5	0.00012
≥5.2	86	24	
$TLG_{2.5}$			
<18.8	103	5	0.00012
≥18.8	86	24	

CR complete response, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

Table 3 Results of multivariate analysis between clinical evaluation and pre-treatment indexes

Prognostic factors	Odds ratio	95 % CI	*p* value
T4	2.73	1.15–6.51	0.0230
N2b	6.96	1.50–32.3	0.0132
N2c	11.80	2.37–58.50	0.00258
$TLG_{2.5}$ ≥18.8	6.25	2.17–18.00	0.000672

CI confidence interval, *TLG* total lesion glycolysis

FDG-PET/PET-CT plays a major role in the management of HNSCC before and after treatment, including CRT. The efficacy of pre-treatment FDG-PET/PET-CT in the evaluation of NM stage, and in determining the presence of other synchronous cancers is absolute. Recently, the results of pre-treatment FDG-PET/PET-CT, including SUV, MTV and TLG, have been applied as a predictive index, in cases of HNSCC [22–25]. However, the literature to date has mainly focused on the primary site, with only three authors reporting its application to neck lymph node(s). One author reported that the SUV_{max} value in the metastatic neck lymph node was found to be a surrogate marker with a predictive value for local recurrence-free survival (LRFS), distant metastasis-free survival and disease-free survival, although the number of cases analyzed was small [23]. The other two authors reported that there were no correlations between SUV_{max} in the metastatic neck lymph node and LRFS on overall survival [24, 25]. In the present study, we focused on the treatment of metastatic lymph node(s) and the initial treatment was restricted to CRT. Multivariate analysis revealed significant differences in clinical evaluations according to pre-treatment variables (N2b, N2c, T4 and $TLG_{2.5}$ ≥18.8). Simply stated, the more advanced and/or more aggressive the tumor in NHSCC patients, the poorer the prognosis for lymph node metastasis after CRT treatment. The concept of TLG was initially suggested by Larson et al. [26], and the values were calculated by multiplying the MTV values by the SUV_{mean}. TLG corresponds to the cell mass of the target lesion associated with FDG uptake and TLG has been suggested to better reflect global metabolic activity in whole tumors, which represents both the functional tumor burden and the biological aggressiveness [26]. TLG was then thought to be a potentially valuable biomarker for predicting prognosis as well as predicting treatment response in certain types of solid tumors [27]. FDG-PET/PET-CT is an indispensable evaluation method prior to the treatment of HNSCC, and TLG can be calculated from the results without any additional stress on the patients. TLG is considered to be a new useful predictive index for the response of metastatic lymph node(s) to CRT treatment.

Conclusions

To evaluate the treatment response for node-positive HNSCC patients after CRT, the clinical outcome was compared with patient characteristics. TLG calculations prior to CRT can be a new useful predictive factor for the response of lymph node(s) to CRT treatment.

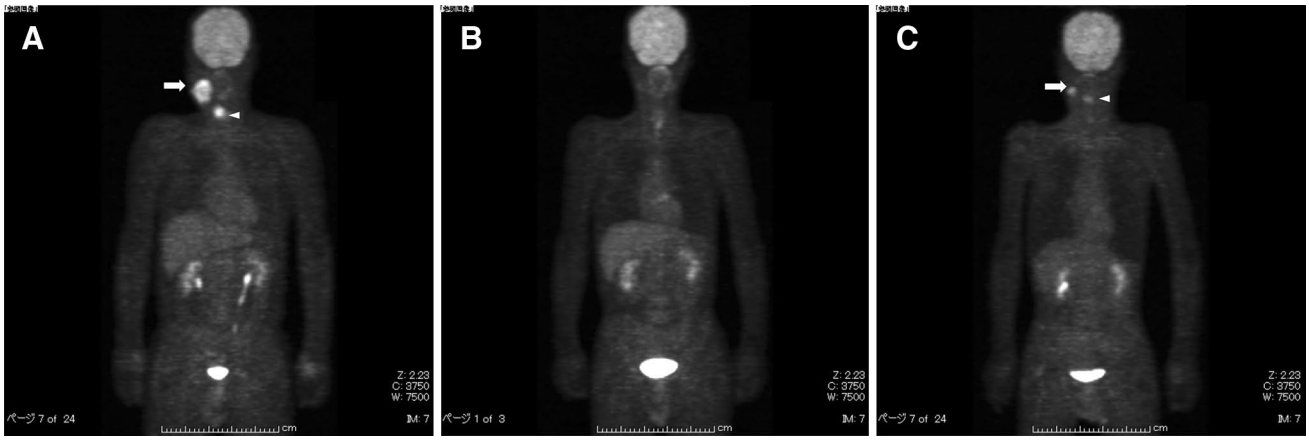

Fig. 2 A 62-year-old male in whom CRT indicated CR at both the primary site and neck lymph node, and recurrence at both sites 7 months after CRT. **a** The primary disease was hypopharyngeal carcinoma, T4aN3M0. The *arrow head* indicates the primary site and the *arrow* indicates lymph node ($MTV_{2.5}$ 60.5, $TLG_{2.5}$ 253.5). **b** 6 weeks after CRT, FDG uptake had disappeared at both the primary site and neck lymph node and these conditions were maintained for 6 months. **c** 7 months after CRT, FDG uptake revealed recurrence at both the primary site (*arrow head*) and lymph node (*arrow*)

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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