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Metabolic tumor volume of metastatic lymph nodes and survival after total laryngectomy in laryngeal and hypopharyngeal cancer

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ABSTRACT

Objectives: The prognostic value of metabolic tumor volume (MTV) in locally advanced laryngeal or hypopharyngeal cancer is established in the setting of chemoradiotherapy, while it remains unknown in the setting of upfront total laryngectomy.

Materials and methods: We retrospectively analyzed 88 patients receiving total laryngectomy and neck dissection, using Cox regression models.

Results and conclusion: Variables related to metastatic lymph node were associated with overall survival, whereas those related to primary tumor were not. In multivariable models, MTV of metastatic lymph nodes (N-MTV) as a continuous variable (Akaike's information criterion (AIC), 277.5) was equivalent to pathological nodal status (AIC, 278.2; $P = 0.40$), and superior to pathological nodal classification as an ordinal variable (AIC, 281.4; $P < 0.05$) in ability of predicting death. The risk of death was increased by 1.2-fold (95% confidence interval (CI), 1.0–1.4; $P = 0.03$) every 10-ml increment of N-MTV, while patients with pN+ disease were at a higher risk of death by 2.9-fold (95% CI, 1.0–12.2; $P < 0.05$) compared with patients with pN0 disease. Using recursive partitioning analysis (RPA), we classified the patients as having a low, intermediate, or high risk of death on the basis of N-MTV and extranodal extension (ENE). This RPA classification system exhibited greater concordance with overall survival than the classification considering pathological nodal status and ENE (AIC, 275.8 versus 281.4; $P = 0.02$). In the setting of upfront total laryngectomy, N-MTV is a critical predictor of mortality. A staging system in which N-MTV is incorporated may better inform adjuvant treatment decisions.

Introduction

Patients with locally advanced laryngeal or hypopharyngeal cancer constitute a subset of squamous cell carcinoma of the head and neck (HNSCC) in sharing larynx preservation as a treatment goal, and are treated with either upfront total laryngectomy or chemoradiotherapy aimed at the larynx preservation. Although guidelines recommend upfront total laryngectomy for patients with T4a tumors [1], it is empirically known that patients with low-volume T4a tumors are well managed with chemoradiotherapy [2]. Moreover, there is considerable interobserver variation in the interpretation of CT images [3], which results in a disagreement in T classification. Accordingly, a volumetric parameter with high interobserver reliability is expected to replace T classification in identifying patients who benefit from the larynx preservation approach.

Positron emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT measures and visualizes metabolic activity. Among quantitative PET measures, volumetric parameters, such as metabolic tumor volume (MTV), which reflect tumor burden with increased FDG uptake, serve as a prognostic factor in various malignancies, including HNSCC [4,5]. We analyzed a consecutive series of patients with stage III/IV laryngeal or hypopharyngeal cancer who had been treated with chemoradiotherapy, though surgical treatment would have required total laryngectomy. We found that the pretreatment MTV of primary

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tumors (T-MTV) was independently associated with laryngectomy-free survival (LFS) and overall survival (OS), whereas MTV of metastatic lymph nodes (LN) (N-MTV) was not [6]. We also found that the inter-observer reliability in measuring MTV was excellent [6]. On the other hand, the prognostic value of MTV in patients undergoing upfront total laryngectomy remains unknown.

In this retrospective study, we aimed to address whether pretreatment T-MTV and/or N-MTV would be predictive of OS in patients with stage III/IV laryngeal or hypopharyngeal cancer receiving upfront total laryngectomy. We also aimed to create a risk stratification system in which MTV was incorporated.

Patients and methods

Patients

Patients with newly diagnosed stage III/IV laryngeal or hypopharyngeal cancer who underwent pretreatment ^{18}F-FDG PET/CT and were treated with upfront total laryngectomy and neck dissection for curative intent between June 2006 and December 2013 at Osaka Medical Center for Cancer and Cardiovascular Disease (current name: Osaka International Cancer Institute) were eligible. Exclusion criteria were blood glucose levels that had deviated from the normal range (80–120 mg/dL) prior to FDG-PET/CT scanning, and a follow-up duration of less than 12 months. Patients who underwent tracheotomy prior to FDG-PET/CT scanning were also excluded because tracheotomy would affect the measurement of T-MTV. All patients were staged according to the UICC TNM staging system (seventh edition) [7]. This study was approved by the Institutional Review Board. Written informed consent was waived because of the retrospective nature of the study.

^{18}F-FDG PET/CT and measurement of MTV

Patients fasted for at least 4 h before intravenous administration of approximately 3.7 MBq/kg of FDG. ^{18}F-FDG PET/CT was performed using integrated scanners (Gemini GXL; Philips, Eindhoven, Netherlands, or Biograph, Siemens, Germany). Whole-body images, generally from the top of the skull to the mid-thigh, were acquired approximately 60 min after intravenous injection of FDG. PET was performed under the following parameters: 3-dimensional emission scan, 2-min scan per bed position × 11 positions, ordered-subset expectation maximisation reconstruction, and 4.0-mm slice thickness per interval. Attenuation correction was performed with CT data. The parameters used for CT acquisition were as follows: breath-hold during normal expiration from the lung apex to the lower poles of the kidneys; no intravenous or oral contrast medium; 120 kVp and 50 effective mA; 16 slices; 1.5-mm detector collimation; and 5.0-mm slice thickness, with a 4.0-mm interval. Coronal and sagittal CT images were reconstructed using axial thin-section CT images of 1.5-mm slice thickness.

FDG-PET/CT data were transferred onto the workstation in the digital imaging and communications in medicine (DICOM) format. PET/CT parameters were measured from attenuation-corrected PET/CT data using a standardized uptake value (SUV)-based automated contouring program (PETSTAT Viewer Version 2.2 [64bit]; Adln Research Inc., Tokyo, Japan), which automatically delineated the region of interest (ROI). The boundary was drawn large enough to incorporate a target lesion in the three imaging planes. To define the margin around the tumor, an SUV threshold of 2.5 was used, and MTV was automatically calculated. No standard SUV threshold exists for volume-based metabolic parameters. Given our finding that an SUV threshold of 2.5 outperformed other thresholds to delineate MTV in the analysis of patients treated non-surgically [6], this SUV threshold was used in this study. Two head and neck surgeons (J.M. and H.I.), who had high expertise in interpreting FDG-PET/CT, determined MTV by consensus with all clinical outcomes blinded. T-MTV and N-MTV were measured independently. When multiple metastatic nodes were found, the MTV of each metastatic node was measured one by one, the sum of which constituted the N-MTV. Whole MTV was defined as the sum of the T-MTV and N-MTV.

Statistical analysis

Univariable and multivariable analyses were performed using the Cox proportional hazards regression model to identify predictors of OS, and the estimated hazard ratio (HR) and 95% confidence interval (CI) were calculated. The suitability of the multivariable models was compared using Akaike's information criterion (AIC) [8]. An event of OS was defined as any death. All events were measured from the date of surgery to the date of their occurrence or the date of the last follow-up visit. OS was estimated by means of the Kaplan–Meier method, and was compared among groups using the log-rank test. Treatment failure rate was calculated using the method of cumulative incidence, with death without treatment failure considered as a competing risk, and was analyzed using the Cox proportional hazards regression model.

Patients were classified according to the recursive partitioning analysis (RPA) method, considering death as the dependent variable and N-MTV and pathological extranodal extension (ENE) as the independent variables. The performance of the RPA classification system in predicting mortality was assessed against the classification system on the basis of pathological nodal status and ENE, using AIC.

The spearman correlation coefficient was used to evaluate the association between MTV and TNM classification. All statistical analyses were performed using JMP v14 statistical software (IBM Japan, Tokyo, Japan) and open source statistical software R (http://www.R-progect.org). Two-tailed *P* values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

We reviewed clinical records and identified 97 patients who met the inclusion criteria. We excluded three patients because of unparseable PET data, five because of tracheotomy prior to FDG-PET/CT scanning, which affected delineation of the ROI, and one because of a follow-up duration of less than 12 months. Finally, 88 patients were included in the analysis. Baseline characteristics of the patients are summarized in Table 1. At the time of analysis, there were 34 deaths: 19 patients died of index cancer, 10 of another cancer, and five of other causes. With a median follow-up of 65 months for surviving patients (range, 28–113 months), the 5-year OS rate for the whole cohort was 61.5% (95% CI, 50.4–71.5). The median interval between FDG-PET/CT and surgery was 18 days (range, 2–59 days). The associations between T-MTV and T classification, N-MTV and N classification, and whole MTV and stage are shown in Fig. 1.

MTV and survival

In the univariable analysis (Table S1 in the Supplement), age as a continuous variable and sex were significant and marginal determinants of OS, respectively, while neither primary tumor site nor postoperative adjuvant therapy were associated with OS. Variables related to the primary tumor, such as clinical and pathological T classification as an ordinal variable and T-MTV as a continuous variable, were not associated with OS. In contrast, variables related to LN metastasis were inconsistently associated. Clinical and pathological nodal status was a marginal and significant determinant of OS, respectively. As for pathological N classification as an ordinal variable, only pN2 disease was at a significantly higher risk of death compared with pN0 disease. Likewise, cN2 disease was at a marginally higher risk. Association of N3

Table 1
Baseline characteristics of patients ($N = 88$).

Characteristic		No.	(%)
Age, years	Median	65	
	Range	40–84	
Gender	Male	82	(93)
	Female	6	(7)
Primary site	Larynx	27	(31)
	Hypopharynx	61	(69)
cT classification	T2	7	(8)
	T3	45	(51)
	T4a	36	(41)
pT classification	T2	6	(7)
	T3	41	(47)
	T4a	41	(47)
cN classification	N0	20	(23)
	N1	12	(14)
	N2a/b/c	5/31/17	(60)
	N3	3	(3)
pN classification	N0	20	(23)
	N1	7	(8)
	N2a/b/c	3/24/31	(66)
	N3	3	(3)
Clinical stage	III	17	(19)
	IVA/B	68/3	(81)
Pathological stage	III	7	(8)
	IVA/B	78/3	(92)
Extranodal extension	Negative	41	(47)
	Positive	47	(53)
Neck dissection	Unilateral	12	(14)
	Bilateral	76	(86)
Adjuvant therapy	No	39	(44)
	Radiotherapy	35	(40)
	Chemoradiotherapy	14	(16)

disease with mortality was less significant, which was most probably because the number of patients with N3 disease was small ($N = 3$). N-MTV as a continuous variable was significantly associated with OS, whereas ENE was not. Clinical and pathological disease stage and whole MTV as a continuous variable were not associated with OS.

We sought to address which variable related to LN metastasis would be most predictive of mortality. To this end, we constructed a series of multivariable models in which each variable related to LN metastasis was incorporated after adjustment for age and primary tumor site: N-MTV model, clinical N classification model, pathological N classification model, clinical nodal status model, pathological nodal status model, and ENE model (Table 2). Given that primary tumor site was an established prognostic factor [9], it was adjusted although it was not associated with OS in our series. Sex was not incorporated in the multivariable models because the balance was highly biased, with females accounting for only 7%. According to AIC, the continuous N-MTV model was equivalent to the pathological nodal status model in predicting death (AIC, 277.5 versus 278.2). The risk of death was increased by 1.2-fold (95% CI, 1.0–1.4; $P = 0.03$) for every 10-ml increment of N-MTV, while patients with pN+ disease were at a higher risk of death by 2.9-fold (95% CI, 1.0–12.2; $P < 0.05$) compared with patients with pN0 disease. On the other hand, the N-MTV model was superior to the clinical N classification model (AIC, 283.7) and pathological N classification model (AIC, 281.4). The outperformance of the N-MTV model over the clinical nodal status model (AIC, 280.0) and ENE model (AIC, 280.5) was less significant, while neither clinical nodal status nor ENE were independently associated with OS. Of note, similar results were obtained in the analysis excluding females ($N = 82$) (data not shown).

MTV-derived risk stratification system

Although ENE was not an independent determinant of OS in our cohort, it is established as a critical adverse risk factor of OS by meta-analysis [10,11]. In addition, a series of evidence has shown that patients with pN0 disease survive better than patients with pN+/ENE− disease, and that patients with pN+/ENE− disease survive better than patients with pN+/ENE+ disease [12–14]. Given that N-MTV as a continuous variable as well as pathological nodal status were independent predictors of OS, it was of interest to examine how the combination of N-MTV and ENE would serve for the risk stratification. Accordingly, we constructed the RPA algorithm (Fig. 2A). N-MTV (< 11.3 ml vs. ≥11.3 ml) was the major determinant of OS, and patients with N-MTV (< 11.3 ml) were further categorized by ENE status. The patients were classified into three categories with respect to the risk of death: low risk (N-MTV < 11.3 ml /ENE-), with a 5-year OS rate of 81.8% (95% CI, 64.7–91.7); intermediate risk (N-MTV < 11.3 ml/ENE+), with a 5-year OS rate of 57.4% (95% CI, 39.5–73.6); and high risk (N-MTV ≥ 11.3 ml), with a 5-year OS rate of 36.1% (95% CI, 18.5–58.5) (Fig. 2B). On the other hand, 5-year OS rates for patients with pN0 disease, patients with pN+/ENE- disease, and patients with pN+/ENE+ disease were 85.0% (95% CI, 62.4–95.1), 61.2% (95% CI, 39.4–79.3), and 53.3% (95% CI, 38.6–67.4), respectively (Fig. 2C). Table 3 shows the results of multivariable analysis of OS after adjustment for age and primary tumor site. The high-risk group showed HRs of 4.1 (95% CI, 1.7–10.8; $P = 0.002$) and 3.0 (95% CI, 1.0–12.7; $P = 0.04$) in the RPA classification system and pN/ECE classification system, respectively. The RPA classification system showed improvement in the ability to predict death over the pN/ENE classification system (AIC, 274.4 versus 280.3).

MTV and treatment failure

We next sought to assess the association of the aforementioned classification systems with treatment failure. Three, 16, and seven patients developed both distant metastasis and locoregional recurrence, distant metastasis alone, and locoregional recurrence alone, respectively. Fig. 3 depicts the cumulative incidences of treatment failure. The difference was more prominent in the RPA classification system than in the pN/ENE classification system, with 5-year cumulative incidence of treatment failure in the low-risk, intermediate-risk, and high-risk groups being 11.9% (95% CI, 3.7–25.4), 31.8% (95% CI, 16.3–48.4), and 52.4% (95% CI, 28.7–71.6), respectively, for the RPA classification system, and 10.0% (95% CI, 1.6–27.8), 24.2% (95% CI, 8.4–44.3), and 38.8% (95% CI, 24.7–52.7), respectively, for the pN/ENE classification system. The results of univariable analysis and multivariable analysis after adjustment for primary tumor site and adjuvant therapy are shown in Table S2 in the Supplement and Table 4, respectively. The RPA classification system exhibited better concordance with treatment failure than the pN/ENE classification system (AIC, 215.3 versus 220.6).

Discussion

In the present study, we demonstrated for the first time that pretreatment N-MTV was an independent predictor of OS in patients with locally advanced laryngeal or hypopharyngeal cancer undergoing upfront total laryngectomy, whereas pretreatment T-MTV was not. This finding was striking, especially given our previous finding that not pretreatment N-MTV but pretreatment T-MTV was an independent predictor of LFS and OS in the same line of patients undergoing larynx preservation chemoradiotherapy. These results prompted us to presume that the prognostic value of T-MTV and N-MTV would differ between surgical and non-surgical approaches, and that T-MTV and N-MTV should be handled separately when evaluating the prognostic value of MTV. In turn, we presume that patients treated surgically and non-surgically should not be combined, and that whole MTV, the sum of T-MTV and N-MTV, should not be used, when evaluating the prognostic value of MTV.

We also demonstrated that the RPA classification system considering N-MTV and ENE served better for the risk stratification,

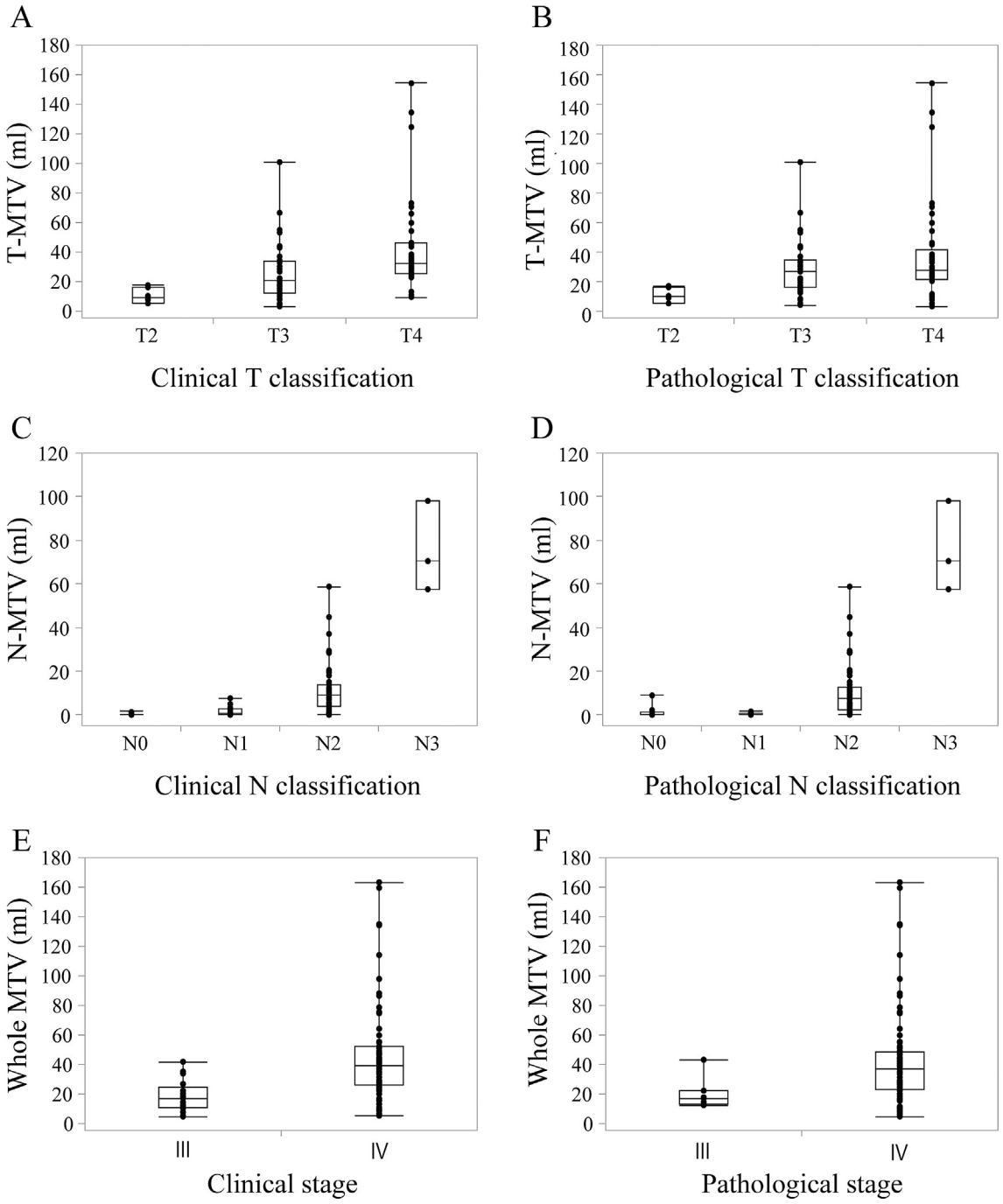

Fig. 1. Association of metabolic tumor volume with TNM classification. Metabolic tumor volume (MTV) of primary tumor as a function of clinical (A) and pathological (B) T classification. MTV of metastatic lymph nodes as a function of clinical (C) and pathological (D) N classification. Whole MTV as a function of clinical (E) and pathological (F) disease stage. Each box contains the center 50% of MTV for each classification or stage. The bar within the box indicates the median. The lines extending above and below each box indicate the range of MTV. Each dot represents an individual MTV. T-MTV was correlated moderately with clinical T classification (spearman correlation coefficient (SpCC), 0.48; $P < 0.0001$), and mildly with pathological T classification (SpCC, 0.25; $P = 0.02$). N-MTV was correlated strongly with clinical N classification (SpCC, 0.75; $P < 0.0001$), and moderately with pathological N classification (SpCC, 0.66; $P < 0.0001$). The association of whole MTV with clinical and pathological stage was moderate (SpCC, 0.46; $P < 0.0001$) and mild (SpCC, 0.24; $P = 0.02$), respectively.

compared with the classification system considering pathological nodal status and ENE. In this context, of note is the recently issued 8th edition of TNM classification, which has incorporated ENE into the criteria for evaluating the regional extension [15]. Ho et al. [16] reported that the RPA classification system considering the number of LN metastasis and ENE exhibited greater concordance with survival than the 8th edition of TNM classification. It would be of great interest to examine which exhibit better prognostic capacity, the RPA classification system considering N-MTV and ENE or the 8th edition of TNM classification. Unfortunately, however, our cohort was not large enough to address this issue. A larger cohort will allow us to classify patients into more fragmented risk-categories on the basis of N-MTV and ENE, and to compare the novel classification system with the 8th edition of TNM classification. Of importance, N-MTV showed an association with neither clinical nor pathological N2 subclassification (N2a/b/c) (Fig. S1 in the Supplement), although mortality risk escalated continuously with

Table 2
Multivariable analysis of overall survival in metastatic lymph node-related models.

Model		Overall survival			
		Hazard ratio	95% CI	*P* value	AIC score
N-MTV	per 10-ml increment	1.2	1.0–1.4	0.03	277.5
cN classification	N0	Reference			283.7
	N1	1.5	0.4–6.4	0.57	
	N2	2.2	0.8–7.4	0.13	
	N3	3.0	0.4–16.0	0.26	
pN classification	N0	Reference			281.4
	N1	1.5	0.2–9.6	0.65	
	N2	3.0	1.1–12.7	0.04	
	N3	4.0	0.5–25.6	0.17	
Clinical nodal status	Negative	Reference			280.0
	Positive	2.1	0.8–7.0	0.15	
Pathological nodal status	Negative	Reference			278.2
	Positive	2.9	1.0–12.2	< 0.05	
Extranodal extension	Negative	Reference			280.5
	Positive	1.6	0.8–3.3	0.20	

AIC, Akaike's information criterion; CI, confidence interval; N-MTV, metabolic tumor volume of metastatic lymph nodes.

increasing N-MTV. Given the excellent interobserver reliability in measuring MTV [6], the classification system considering N-MTV and ENE may have the potential to augment staging.

Two randomized trials established level I evidence that the addition of concomitant cisplatin to postoperative radiotherapy improves locoregional control and disease-free survival of patients with locally advanced HNSCC [17,18]. A retrospective subgroup analysis showed that patients who had two or more histopathologically involved LNs without ENE did not benefit from the addition of chemotherapy [19]. The RPA classification system defined patients with large (≥11.3 ml) N-MTV disease at a high risk of death irrespective of ENE status. Of 21 patients belonging to this high-risk group, six had ENE- disease, three of whom had treatment failure. Given that none of the three patients received chemoradiotherapy in the adjuvant setting (data not shown), the addition of systemic chemotherapy to postoperative radiotherapy might have improved their disease-free survival. The classification system considering N-MTV and ENE could be helpful in adjuvant treatment decision-making, which needs to be validated prospectively.

We found that T-MTV was not associated with OS in patients receiving upfront total laryngectomy, in contrast to our previous finding that T-MTV was independently associated with LFS and OS in patients receiving chemoradiotherapy in the setting of larynx preservation [6]. Although the reason why the predictive value of T-MTV might differ between surgical and non-surgical approaches remains unknown, these findings imply that T-MTV would aid the treatment decision-making on locally advanced laryngeal and hypopharyngeal cancer, in addition to other considerations such as laryngeal function. It would make sense not to recommend larynx-preservation chemoradiotherapy for patients with large T-MTV disease and/or with impaired laryngeal function. We believe that these patients are encouraged to undergo total laryngectomy, although an optimal cutoff defining large T-MTV needs to be established.

Our study has some limitations. First, it was a retrospective analysis of a relatively small cohort. Second, all the patients received total laryngectomy and neck dissection, whereas adjuvant therapy was heterogeneous. Third, although the measurements of MTV are extremely reproducible [6], the harmonization of imaging procedures is required to generalize the measurement of MTV across different PET systems [20], which can hamper the spread of an MTV-derived risk stratification system.

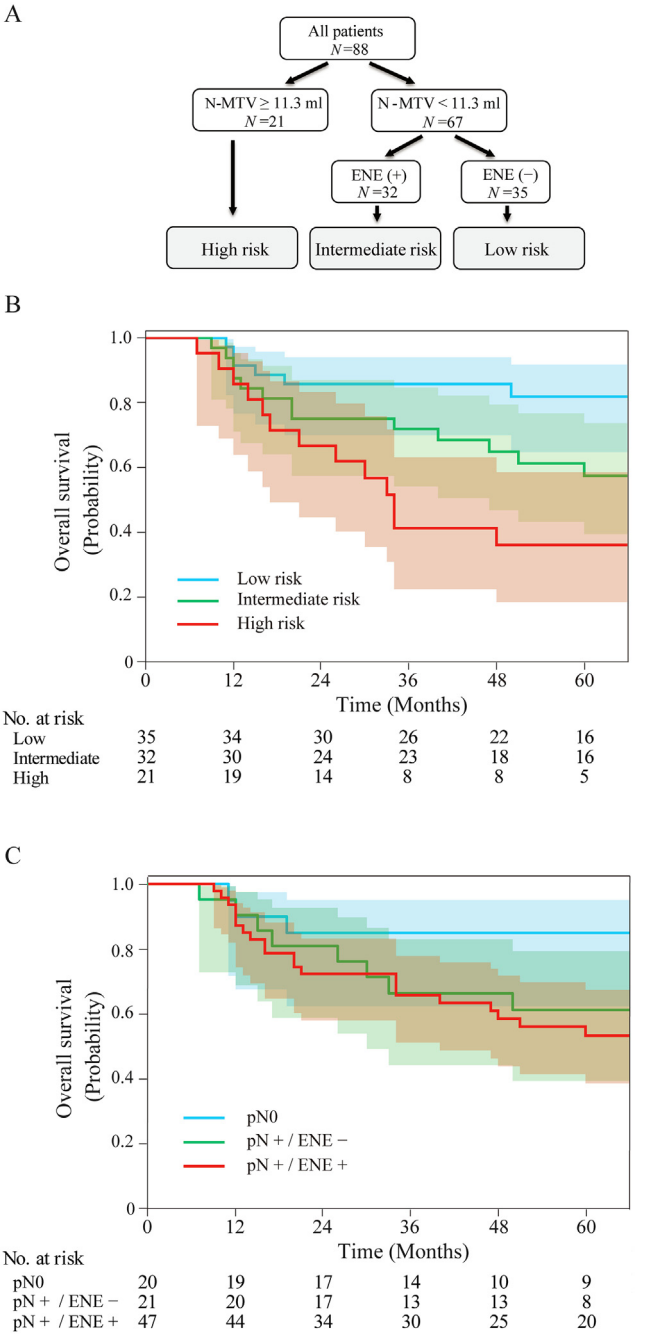

Fig. 2. Nodal classification system and survival. (A) Novel nodal classification system was developed by RPA to classify patients into categories of low, intermediate, or high risk of death with N-MTV and ENE being prognostic factors. Kaplan-Meier estimates of overall survival according to (B) the RPA-classification system and (C) pN/ENE classification system are displayed along with 95% confidence intervals. ENE, extranodal extension; N-MTV, metabolic tumor volume of metastatic lymph nodes; pN, pathological nodal status; RPA, recursive partitioning analysis.

In conclusion, the prognostic value of T-MTV and N-MTV differs between surgical and non-surgical approaches in the treatment of patients with locally advanced laryngeal or hypopharyngeal cancer requiring total laryngectomy. N-MTV, but not T-MTV, is a critical predictor of mortality in the setting of total laryngectomy. Combination of N-MTV with ENE may lead to the development of a novel staging system. The validation in a larger cohort is expected to draw firm conclusions.

Table 3
Multivariable analysis of overall survival for nodal classification systems.

Classification system	Risk group	No. of patients	No. of events	Overall survival			AIC score
				Hazard ratio	95% CI	*P* value	
RPA-derived	Low	35	7	Reference			274.4
	Intermediate	32	13	2.0	0.8–5.5	0.12	
	High	21	14	4.1	1.7–10.8	0.002	
pN and ENE	pN0	20	3	Reference			280.3
	pN + /ENE-	21	9	2.7	0.8–12.2	0.12	
	pN + /ENE +	47	22	3.0	1.0–12.7	0.04	

AIC, Akaike's information criterion; CI, confidence interval; ENE, extranodal extension; pN, pathological nodal status; RPA, recursive partitioning analysis.

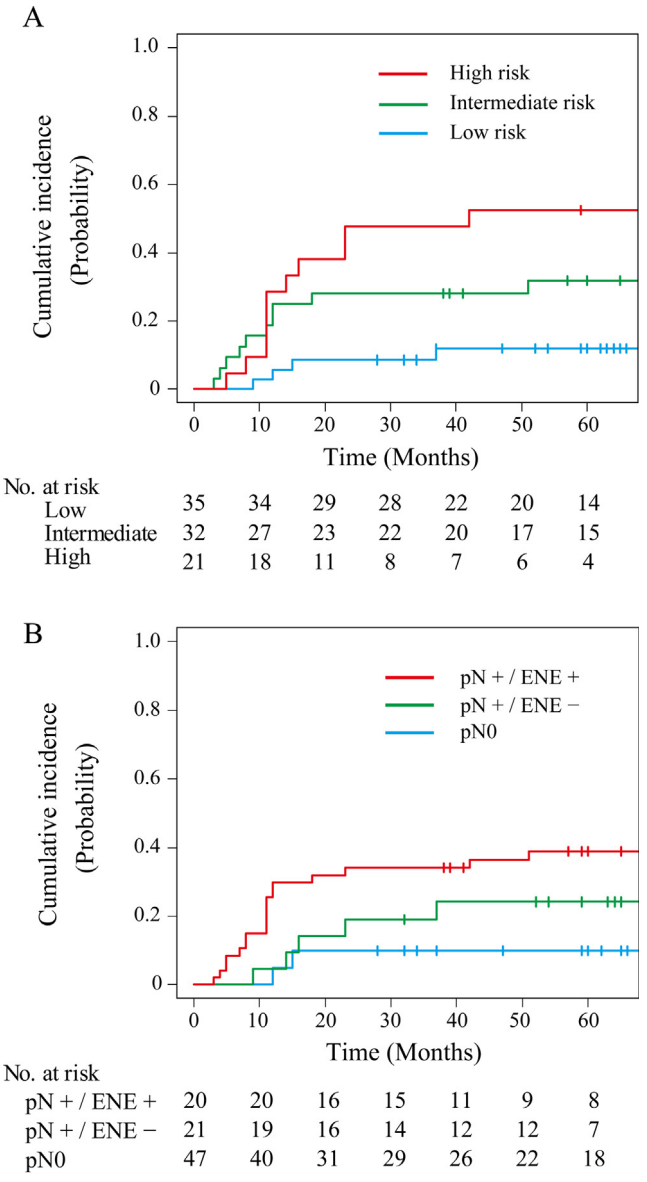

Fig. 3. Cumulative incidence of treatment failure for (A) the recursive partitioning analysis-nodal classification system and (B) the nodal classification system based on pathological nodal status and extranodal extension. Death without treatment failure was considered as a competing risk.

Table 4
Multivariable analysis of treatment failure for nodal classification systems

Classification system	Risk group	Overall survival			AIC score
		Hazard ratio	95% CI	*P* value	
RPA-derived	Low	Reference			215.3
	Intermediate	4.4	1.4–16.7	0.01	
	High	8.2	2.5–31.9	0.0004	
pN and ENE	pN0	Reference			220.6
	pN + /ENE-	3.0	0.6–21.7	0.19	
	pN + /ENE +	6.2	1.5–41.7	0.009	

AIC, Akaike's information criterion; CI, confidence interval; ENE, extranodal extension; pN, pathological nodal status; RPA, recursive partitioning analysis.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.04.011.

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