Title: New proposal to revise classification for squamous cell carcinoma of external auditory canal and middle ear

Running title: New classification for ear cancer

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Abstract

Background: Prognosis of the patients with advanced squamous cell carcinoma of external auditory canal and middle ear (SCC-EAC/ME) have been improved by advances in skull base surgery and multidrug chemoradiotherapy during the last two decades.

Methods and Patients: Ninety-five patients with SCC-EAC/ME who were treated between 1998 and 2017 were enrolled. The number of the patients with T1, T2, T3 and T4 were 15, 22, 24, 34, respectively. Oncological outcomes and prognostic factors were retrospectively investigated.

Results: Among patients with T4, brain invasion (p=0.024), carotid artery and/or jugular vein invasion (p=0.049, 0.040) were found as significant poor prognostic factors. The 5-year overall survival rate of the patients with at least one of these factors (T4b) was significantly higher than that of the patients without these factors (T4a) (65.5% vs 25.5%, p=0.049).

Conclusions: We would like to propose to subclassify T4 into T4a and T4b according to the prognostic factors.

(149 words)

Key Words: auditory canal cancer, temporal bone cancer, lateral temporal bone resection, classification, prognosis

Introduction

Squamous cell carcinoma of external auditory canal and middle ear (SCC-EAC/ME) is an extremely rare entity with an annual incidence estimated at between 1 to 6 cases per million of the populations.[1)] While early SCC-EAC has been successfully treated by sleeve resection or lateral temporal bone resection (LTBR), more advanced cancer requires subtotal temporal resection (STBR) resulting in facial palsy, hearing impairment and balance disorder with severe postoperative complications such as cerebral infarction and meningitis.

The modified Pittsburgh classification proposed by Moody et al[2)] in 2000 have been most commonly used for SCC-EAC/ME. In Moody's classification, tumors limited in temporal bone are defined as T1 or T2. Tumors extending to middle ear or apparently eroding temporal bone defined as T3. Tumors with invasion into cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen or dura, or with extensive soft tissue involvement, such as TMJ(temporomandibular joint) or styloid process or evidence of facial paresis are defined as T4. Thus, T4 covers a fairly wide range from small extent to the middle ear wall to highly extent to the brain. According to this classification, while reported oncological results of the patients with T1, T2, and T3 were favorable, survival rates of the patients with T4 were extremely poor[3)-7)] by the late twentieth century. However, during the last two decades, advances in surgical techniques for skull base surgery and multidrug concomitant chemoradiotherapy (CRT) with docetaxel, cisplatin and 5 fluorouracil (TPF-RT) have improved oncological results for patients with advanced SCC-EAC/ME, especially when oncological resection is

feasible[8)-10)]. Then again, prognoses of the patients with unresectable T4 were still quite poor. Considering these backgrounds, in this study, we investigated the prognostic factors for patients with advanced SCC-EAC/ME to update the staging system and ensure ongoing relevance with advances in surgical and non-surgical treatments.

Materials and Methods

Patients

Between 1998 and 2017, 102 consecutive patients with SCC-EAC/ME were treated at Kobe University Hospital. Among the 102 patients, we retrospectively reviewed 95 patients who were pathologically diagnosed as SCC-EAC/ME and treated with curative intent. The remaining 7 patients were excluded from this study. Two patients aged 90 or older refused definitive therapy and were treated by palliative radiotherapy for pain relief. Three patients simultaneously had other advanced cancer and were also had palliative radiotherapy as best supportive care. The other two patients with severe dementia also could not have treatment with curative intent. Patients who had unresectable tumors and had undergone non-surgical treatment were considered to have undergone radical treatment and were included in this study.

Diagnosis and Treatments

At the initial diagnosis, extent of disease was assessed with the aid of contrast computerized tomography scan (CT), magnetic resonance imaging (MRI), and 18-fluoro-2-deoxyglucose positron emission tomography (FDG-PET). Diseases were staged according to the most recent

version of the modified Pittsburgh classification (2000)[2]. Sites of invasion were determined by preoperative imaging study.

For patients with T1 and T2, principally we recommended surgical treatment. Radiotherapy (RT) was employed for patients who refused surgery. Sleeve resection or lateral temporal bone resection (LTBR) was performed for T1 and T2 diseases. For patients with T3, we recommended subtotal temporal bone resection (STBR) or LTBR depending on the extent of the disease. When patients refused surgery, concurrent chemoradiotherapy (CRT) with cisplatin or combination of TPF [8] was recommended. For patients with resectable T4 disease, we recommended STBR. Invasion to carotid artery and extensive dural invasion were considered as contraindication, while minor dural and/or brain invasion was considered as resectable. For patients with unresectable T4 disease and patients who refused STBR, CRT with cisplatin or combination of TPF [8] was performed. Particle beam therapy (carbon or proton) was employed in patients who strongly requested this therapy. Postoperative radiotherapy (PORT) was given to the surgically treated patients with positive or close surgical margin.

Surgery Procedures

In LTBR, principally, the bony external auditory canal, tympanic membrane, malleus and incus were resected with extended mastoidectomy in en bloc manner. Superficial lobe of the parotid gland was resected in 3 out of 11 in T1 and 12 out of 20 in T2. If parotid gland invasion or parotid lymph node involvement was identified, total parotidectomy

was performed. Facial nerve was preserved in all cases. Neck dissection was not performed in any case of LTBR.

In STBR, after total parotidectomy and prophylactic neck dissection (Level II-III), temporal bone was resected in en bloc manner with temporo-suboccipital craniotomy. Resection lines were anteriorly internal carotid artery and posteriorly sigmoid sinus. Medial resection line was internal auditory canal. Mandibular condyle was removed to obtain surgical field and facial nerve was sacrificed. Principally, jugular bulb, sigmoid sinus and dura were preserved, but were resected according to the extent of disease. Defect was reconstructed using rectus abdominis musculocutaneous free flap. Tumors with extension to the carotid artery, extensive dura, and/or brain were considered as contraindication for STBR. While tumors with limited infiltration to the jugular vein could be successfully resected by sacrificing the jugular vein in selected cases, it was often difficult to ensure a negative surgical margin in most cases. Thus, we consider tumors with invasion to jugular vein as relatively inoperable. Limited dural invasion, TMJ invasion and facial nerve invasion were judged as resectable. Our treatment strategies were summarized in Table 1.

Statistical analysis

Medical records were retrospectively reviewed to obtain information concerning characteristics of the patients, extent of disease, treatment, surgical procedures, surgical margin, PORT, treatment period and oncological results. Treatment period was divided into the former term

(1998-2005) and the latter term (2006-2017), since we started to apply TPF-RT to the patients with SCC-EAC/ME from 2006 when applicable. Kaplan-Meier plots were used to summarize time to event measured from the end of the first treatment. The log-rank test was used for univariate analysis on survival rates, and the Cox proportional hazards regression analysis was used for multivariate analysis on survival rates. A *P* value of 0.05 or less was defined as a significant difference. R software (Ver. 3.0.2. 2013. The R foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis. This study was approved by Kobe University Hospital Internal Review Board.

Results

The characteristics of the patients were summarized in Table 2. The age of the patients ranged from 38 to 94 years old with a median age of 64 years. Follow-up periods ranged from 7 to 144 months (median: 50 months, average: 49.7 months). According to T classification, the numbers of the patients with T1, T2, T3 and T4 were 15, 22, 24, and 34, respectively. Only 6 patients had metastatic lymph nodes. Most common treatment was surgery which was selected mainly for early stage diseases. Among T1 and T2 patients, 11 patients out of 15 patients in T1 and 20 patients out of 22 patients had surgical resection, while 5 patients underwent RT alone and only one patient underwent proton beam therapy. Among T3 patients, 11 patients had surgical resection, 6 patients underwent CRT, 6 patients underwent RT alone, and one patient underwent proton beam therapy. Among T4 patients, 9 patients had surgical resection, 20 patients underwent CRT (CDDP 12, TPF 8), 5 patients underwent RT alone,

and one patient underwent proton beam therapy.

Patients treated with (chemo-)radiotherapy were summarized in Table 3. Fifteen patients were treated with RT alone. Eighteen patients were treated with CDDP-based CRT and eight patients were treated with TPF-RT. Three patients had proton beam therapy. Nineteen patients had PORT.

Details of univariate analysis on survival rates are summarized in Table 4. The significant difference was found in original site ($p=0.011$), T classification ($p<0.001$), status of surgical margin ($p=0.001$), PORT ($p=0.004$), and treatment period ($p=0.013$), though status of surgical margin was obtained from medical records in 46 out of 51 surgically treated patients. The results of multivariate analysis for 46 surgically treated patients whose information of surgical margin was available were shown in Table 5a and the results of all 95 patients were shown in Table 5b. Regardless of treatment modality, T classification (T4) was found as a significant independent prognostic factor. Treatment period was also found as a significant independent prognostic factor.

The 5-year overall survival (OS) rates of the patients with T1, T2, T3 and T4 were 93.3%, 95.2%, 84.7% and 42.9%, respectively. The 5-year disease-specific survival (DSS) rates of the patients with T1, T2, T3 and T4 were 100%, 100%, 84.7% and 48.3% respectively. Kaplan-Meier plots of overall survival according to T classification were shown in Figure 1. According to the survival curve, survival rate of patients with T4 was especially worse than the survival rates of patients with T1, T2 and T3. Thus, next, we further analyzed the prognostic factors for patients with T4 in detail.

The results of univariate analysis according to invasion sites of 34 patients with T4 were shown in Table 6. Brain invasion (p=0.024), internal carotid artery invasion (p=0.049), and internal jugular vein invasion (p=0.040) were found as poor prognostic factors. From these results, we subclassified T4 disease invading to brain invasion, carotid artery or jugular vein as T4b, and T4 disease without these features as T4a. Characteristics of T4a and T4b patients were shown in Table 7. (Chemo-) radiotherapy tended to be applied in patients with T4b, since most of T4b diseases were unresectable. The Kaplan Meier curves of patients with T4a and T4b as well as T1, T2 and T3 were shown in Figure 2. The overall survival rate of T4a was significantly higher than that of T4b (65.5% vs 25.5%, p=0.049). Furthermore, we compared the overall survival rate of patients undergoing CRT. The overall survival rate of T4a patients undergoing CRT was significantly higher than that of T4b patients undergoing CRT (5-year-OS-rate 100% VS 36.4%, p=0.020).

Discussion

Due to its rarity and aggressive oncological behavior, standard treatment for SCC-EAC/ME has not been established yet. For most reported cases, treatment consisting of surgical resection and postoperative RT has been selected.[5)-7),11)-15)] While cure rates of the early lesions (T1 and T2) treated by en bloc resection were near to 100%,[11)-15)] treatment of locally advanced cancers are still challenging. In previous literatures, T classification has been reported as most important prognostic factor, since local recurrence is a cause of death in most cases of SCC-EAC/ME. T classification[5),15)-18)], N classification[15),17)], surgical margin[5),16),17)], dural invasion[18)], facial palsy[5),18)], and post-operative radiotherapy[17)] were described as prognostic factors of patients with SCC-EAC/ME as previously reported. In the present study, T classification of modified Pittsburgh staging system was also confirmed as prognostic factor by multivariate analysis of all 95 patients. Of note, oncological outcome of the patients with T4 was extremely poor compared with those of patients with T1, T2 and T3. The 5-year OS rate of patients with T4 was 42.9%, while those of patients T1, T2 and T3 were 93.3%, 95.2%, 84.7%, respectively. However, reflecting the recent advances in surgical techniques, surgical navigation system and diagnostic imaging, oncological outcome of SCC-EAC/ME has gradually improved. In 1970s, Lewis reported

5-year OS rate of 25% in review of 100 cases.[19] On the other hand, Yin reported 5-year OS rate of 66% in 2006.[5] In meta-analysis, 5-year OS rates of patients with T3 and T4 were 57.5% and 22.9%, respectively in the period of 1976-2008.[20] Those increased up to 72.5% and 35.8%, respectively in the period of 2006-2013.[21] In addition, TPF-RT have provided the promising oncological outcome of advanced SCC-EAC/ME including unresectable far advanced cancers.[8)-10)] These reports and ours demonstrate the necessity for revising TNM classification.

Mazzoni[22] proposed to divide T3 of modified Pittsburgh classification into T3a (tumour extending < 5mm from cartilage to periauricular soft tissues, or tumor strictly limited to the anterior bone wall and growing < 5mm into the parotid space) and T3b (same as for T3a, but extending > 5mm). Also, they divided T4 into T4a (tumour growing into mastoid, without facial nerve paresis) and T4b (tumour growing into mastoid with facial paresis, or infratemporal space, or medial wall of tympanum, labyrinth, petrous bone). Although Mazzoni's classification is useful in case of surgical resection, there were no consideration for resectable and unresectable tumors treated by intensified chemoradiotherapy such as TPF-RT as shown in the present and our previous studies [8,9,10]. To address this limitation, we subclassified T4 disease into two subclasses according to the prognostic factors, brain invasion, internal

carotid artery invasion and internal jugular vein invasion. As shown in Figure 2, patients with T4 was clearly divided to the patients without these factors (T4a) and patients with at least one of these factors (T4b). As majority of T4b diseases were unresectable, patients with T4b were mostly treated with RT or CRT. However, oncological outcomes of the patients with T4b treated by intensive CRT (TPF-RT) was still poor. On the other hand, almost all T4a diseases were oncologically resectable, and 5-year OS rates of patients with T4a treated by intensified CRT were 100%. Our new classification of T4a and T4b may be useful not only for predicting prognosis but also for predicting therapeutic effects.

In the present series, treatment period was also found as a significant independent prognostic factor by multivariate analysis. The most possible reason for the improved oncological outcome with time is the change of our treatment policy for non-surgical treatment from CDDP-CRT to TPF-CRT. Advances in imaging and surgical technique supported by surgical navigation might also contribute to the improved survival, as shown in the meta-analysis[21].

One of the limitations of the present study is a retrospective feature which may contain several biases in terms of choice of treatment and patient selection. Although, the present study is one of the largest series as a single-institute

report based on the long-term follow-up as far as we know, the number of the patients was still small. Currently, we are conducting multi-institutional retrospective study to draw more definitive conclusion.

Conclusion

We propose a new classification classifying T4 of modified Pittsburgh classification into two groups according to the prognostic factors; brain, internal carotid artery, and jugular vein.

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Tables and Figure

Table 1 The treatment strategies of our institute

T stage	Recommend treatment	Treatment option	parotidectomy	Prophylastic ND
T1	Sleeve LTBR	RT alone	None	None
T2	LTBR	RT alone	Superficial paratidectomy	None
T3	STBR (LTBR)	～2006 CDDP-CRT 2007～ TPF-CRT	Total parotidectomy	Level II-III Level II-III
T4 operable	STBR	～2006 CDDP-CRT 2007～ TPF-CRT	Total parotidectomy	Level II-III
T4 inoperable	～2006 CDDP-CRT 2007～ TPF-CRT	- -	-	-

Abbreviation: LTBR; lateral temporal bone resection, STBR; subtotal temporal bone resection, CDDP-CRT; chemoradio theraphy with Cisplatin, TPF-CRT; chemoradio theraphy with Dosetaxel, 5-FU, and Cisplatin, RT; Radiotheraphy, ND; Neck Dissection

Table 2

A:The characteristics of the patients

		Number of patients (%)
Age		Median: 64y (range 38y-94y)
Sex		
	Male	35 pts (39%)
	Female	60 pts (61%)
T classification		
	T1	15 pts (16%)
	T2	22 pts (23%)
	T3	24 pts (25%)
	T4	34 pts (36%)
Lymph-node metastasis		
	Negative	89 pts (93%)
	Positive	6 pts (7%)
Side		
	Right	44 pts (46%)
	Left	51 pts (54%)
Treatment		
	Ope only	32 pts (33%)
	Ope+RT	14 pts (15%)
	Ope+CRT	5 pts (5%)
	RT only	15 pts (16%)
	Proton beam therapy	3 pts (3%)
	CRT	26 pts (27%)
Neck dissection	+	15 pts
	-	36 pts
Clinical lymph-node metastasis	+	6 pts
	-	89 pts

B: Treatment method according to each T stage

T stage	Operation			RT only	CRT	Proton
	Ope only	Ope+RT	Ope+CRT			
T1	9	2	0	4	0	0
T2	18	2	0	1	0	1
T3	3	7	1	6	6	1
T4	2	3	4	4	20	1

Abbreviation: Ope; operation, RT; radiothetrapy, CRT; concomitant chemoradiotherapy

Table 3 Summary of patients treated with radiotherapy

		Definitive RT	Post-operative RT
Concomitant therapy		44 pts	19 pts
	RT alone	15 pts	14pts
	Proton beam alone	3 pts	0 pt
	Cisplatin	18 pts	5 pts
	TPF	8 pts	0 pt
RT fields			
	Primary	16 pts	6 pts
	Primary+neck	28 pts	13 pts
RT method			
	3D-RT	33 pts	13 pts
	IMRT	8 pts	6 pts
	Proton beam	3 pts	0 pt
RT dose (Gy)			
	Mean (SD)	66.6 (4.4)	61.4 (7.1)
	Median (Range)	66 (45-70)	60 (44-70)

Abbreviation: RT; radiation therapy, TPF; cisplatin+docetaxel+5-FU, IMRT; intensity modulated radiation therapy

Proton beam therapy was excluded from RT dose.

Table 4 Univariate analysis on survival rates

		No.of Pts	5-year OS	P value
Age	65 yo or older	46	80.3%	0.92
	Less than 65 yo	49	69.3%	
Original Site	External Auditory Canal	85	76.0%	**0.011**
	Middle ear	10	56.0%	
T classification	T1	15	93.3%	**0.001>**
	T2	22	95.2%	
	T3	24	84.7%	
	T4	34	42.9%	
Lymph node metastasis	N positive	6	54.2%	0.081
	N negative	89	74.4%	
Treatment	Ope only	32	96.8%	0.10
	Ope+PORT	19	60.1%	
	CRT	26	68.0%	
	RT	15	50.0%	
	Proton	3	50.0%	
Surgical margin	Positive	7	53.6%	**0.001**
	Negative	39	94.4%	
	No data	5		
PORT	Yes	19	60.1%	**0.004**
	No	32	96.8%	
Treatment Period	1998-2006	31	64.5%	**0.013**
	2007-2017	64	78.5%	

Abbreviation 5-y-OS rates; 5 years overall survival rates, yo; years old CRT; concomitant chemoradiotherapy, RT; radiotherapy, PORT; post-operative radiotherapy

Table 5

a: Multivariate analysis for 51 operated patients

		HR	CI 95%	P value
T classification	<4 vs 4	12.5	2.2-70.3	**0.004**
Surgical margin	negative vs positive	7.82	0.60-95.0	0.11
PORT	no vs yes	1.90	0.18-19.7	0.59

Status of surgical margin was obtained only in 46 patients.

b: Multivariate analysis for all 95 patients

		HR	CI 95%	P value
T classification	<4 vs 4	5.98	2.58-13.8	**<0.001**
Treatment period	Previous term vs. Latter term	0.36	0.16-0.80	**0.013**

Abbreviation: PORT; post-operative radiotherapy, HR; hazard ratio, CI; confidence interval

Table 6 Univariate analysis of T4 patients according to invasion sites

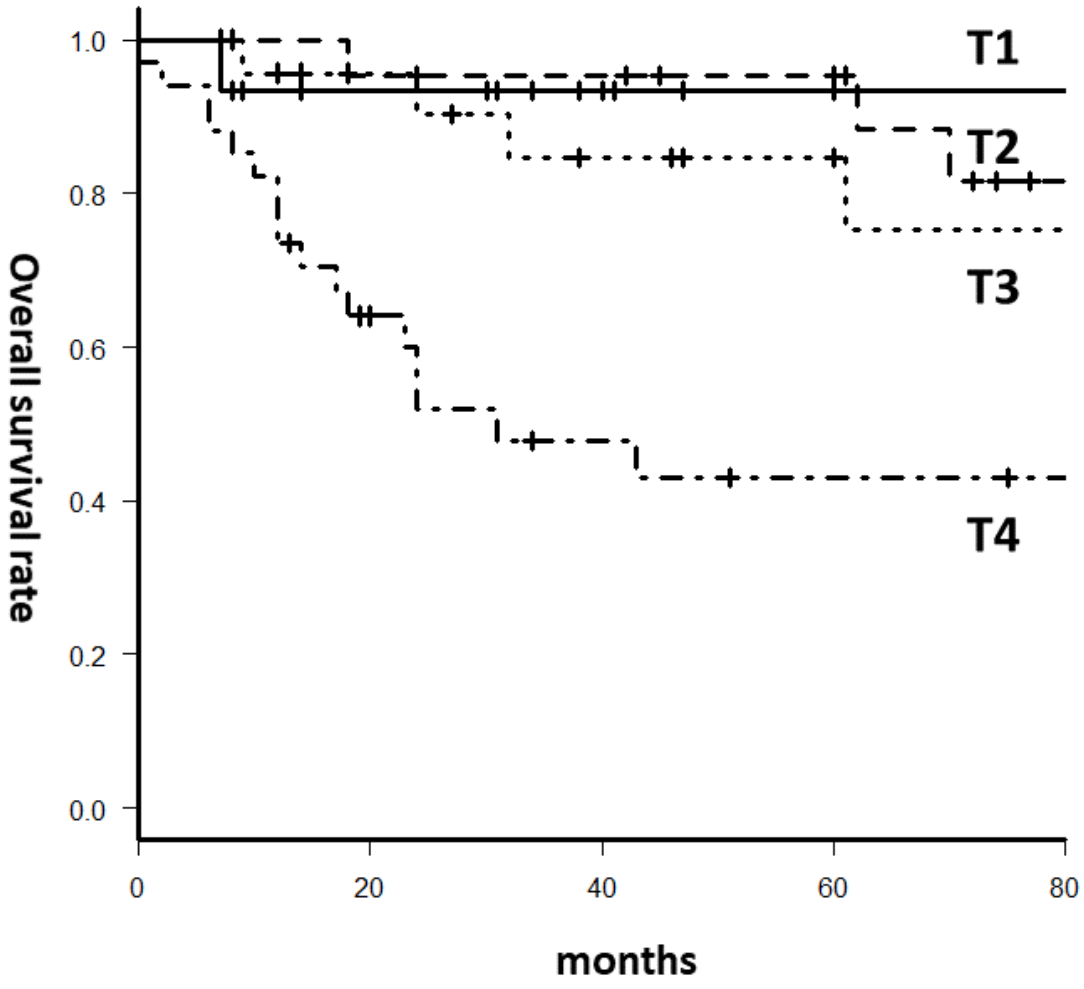
Invasion site		Number of patients	5-year OS	P value
Brain	+	6	No patient	**0.024**
	-	28	48.4%	
Internal carotid artery	+	10	20.0%	**0.049**
	-	24	55.6%	
Internal jugular vein	+	14	16.3%	**0.040**
	-	20	70.0%	
Dura	+	19	39.7%	0.37
	-	15	48.9%	
Facial nerve	+	9	37.0%	0.84
	-	25	46.0%	
Temporal subcutaneous	+	4	100%	0.18
	-	30	38.9%	

Table 7 Characteristics of T4a and T4b patients

		T4a (n=17)	T4b (n=17)	P value
N stage	N+	1 pts	3 pts	0.60
Therapy	Operation	7 pts	2 pts	0.11
	CRT	9 pts	11 pts	
	RT	1 pt	3 pts	
	proton	0 pt	1 pts	
Invasion site	Brain	0 pt	6 pts	**0.018**
	Internal carotid artery	0 pt	10 pts	**<0.001**
	Jugular vein	0 pt	12 pts	**<0.001**
	Dura	8 pts	11 pts	0.49
	Facial nerve	3 pts	6 pts	0.43
	Temporal subcutaneous	4 pts	0 pt	0.10
Resectability	resectable	16 pts	4 pts	**<0.001**
	unresectable	1 pts	13 pts	
5-year overall survival rate		65.5%	25.5%	**0.049**

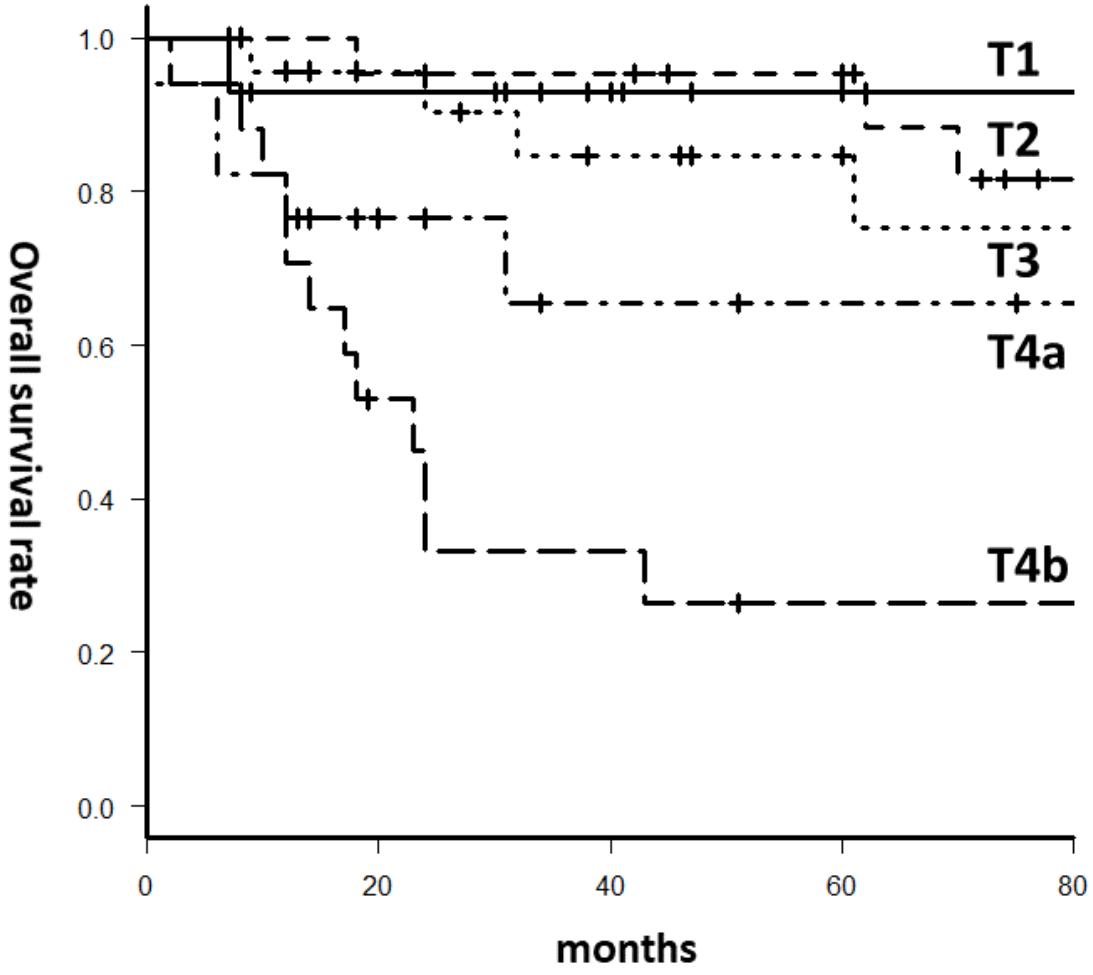
Abbreviations; CRT; chemoradio therapy, RT; radiotherapy

Figure 1 The Kaplan-Meier curves according to T classification of modified Pittsburgh classification



survival rate of patients with T4 was especially worse than the survival rates of patients with T1, T2 and T3.

Figure 2 The Kaplan Meier curves of new classification



The 5-year survival rate of T4a was significantly higher than that of T4b (65.5% vs 25.5%, p=0.049)

Bullet Point Summary

- It is already well known that the Modified Pittsburgh T classification is useful in predicting the prognosis of squamous cell carcinomas arising from an auditory canal.
- Brain invasion (p=0.024), internal carotid artery invasion (p=0.049), and internal jugular vein invasion (p=0.040) were found as poor prognostic factors among the patients with T4.
- Based on that poor prognostic factors, we proposed that a new classification classifying T4 of modified Pittsburgh classification into two groups (T4a and T4b).
- The overall survival rate of T4a was significantly higher than that of T4b (65.5% vs 25.5%, p=0.049).
- Our new classification of T4 may be useful not only for predicting prognosis but also for predicting therapeutic effects.

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