



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

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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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7

1 **Abstract**

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

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

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

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

17 (149 words)

18

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

1 **Introduction**

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

10 The modified Pittsburgh classification proposed by Moody et al²⁾
11 in 2000 have been most commonly used for SCC-EAC/ME. In Moody's
12 classification, tumors limited in temporal bone are defined as T1 or
13 T2. Tumors extending to middle ear or apparently eroding temporal bone
14 defined as T3. Tumors with invasion into cochlea, petrous apex, medial
15 wall of middle ear, carotid canal, jugular foramen or dura, or with
16 extensive soft tissue involvement, such as TMJ(temporomandibular joint)
17 or styloid process or evidence of facial paresis are defined as T4. Thus,
18 T4 covers a fairly wide range from small extent to the middle ear wall
19 to highly extent to the brain. According to this classification, while
20 reported oncological results of the patients with T1, T2, and T3 were
21 favorable, survival rates of the patients with T4 were extremely poor³⁾⁻⁷⁾
22 by the late twentieth century. However, during the last two decades,
23 advances in surgical techniques for skull base surgery and multidrug
24 concomitant chemoradiotherapy (CRT) with docetaxel, cisplatin and 5
25 fluorouracil (TPF-RT) have improved oncological results for patients
26 with advanced SCC-EAC/ME, especially when oncological resection is

feasible⁸⁾⁻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 TPF⁸⁾ 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 TPF⁸⁾ 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

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

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

20

21 **Statistical analysis**

22 Medical records were retrospectively reviewed to obtain information
23 concerning characteristics of the patients, extent of disease, treatment,
24 surgical procedures, surgical margin, PORT, treatment period and
25 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,

1 and one patient underwent proton beam therapy.

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

7 Details of univariate analysis on survival rates are summarized
8 in Table 4. The significant difference was found in original site
9 ($p=0.011$), T classification ($p<0.001$), status of surgical margin
10 ($p=0.001$), PORT ($p=0.004$), and treatment period ($p=0.013$), though status
11 of surgical margin was obtained from medical records in 46 out of 51
12 surgically treated patients. The results of multivariate analysis for
13 46 surgically treated patients whose information of surgical margin was
14 available were shown in Table 5a and the results of all 95 patients were
15 shown in Table 5b. Regardless of treatment modality, T classification
16 (T4) was found as a significant independent prognostic factor. Treatment
17 period was also found as a significant independent prognostic factor.

18 The 5-year overall survival (OS) rates of the patients with T1,
19 T2, T3 and T4 were 93.3%, 95.2%, 84.7% and 42.9%, respectively. The
20 5-year disease-specific survival (DSS) rates of the patients with T1,
21 T2, T3 and T4 were 100%, 100%, 84.7% and 48.3% respectively. Kaplan-Meier
22 plots of overall survival according to T classification were shown in
23 Figure 1. According to the survival curve, survival rate of patients
24 with T4 was especially worse than the survival rates of patients with
25 T1, T2 and T3. Thus, next, we further analyzed the prognostic factors
26 for patients with T4 in detail.

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

1 Discussion

2 Due to its rarity and aggressive oncological behavior, standard
3 treatment for SCC-EAC/ME has not been established yet. For most
4 reported cases, treatment consisting of surgical resection and
5 postoperative RT has been selected.^{5)-7),11)-15)} While cure rates
6 of the early lesions (T1 and T2) treated by en bloc resection
7 were near to 100%,¹¹⁾⁻¹⁵⁾ treatment of locally advanced cancers
8 are still challenging. In previous literatures, T
9 classification has been reported as most important prognostic
10 factor, since local recurrence is a cause of death in most cases
11 of SCC-EAC/ME. T classification^{5),15)-18)}, N classification^{15),17)},
12 surgical margin^{5),16),17)}, dural invasion¹⁸⁾, facial palsy^{5),18)},
13 and post-operative radiotherapy¹⁷⁾ were described as prognostic
14 factors of patients with SCC-EAC/ME as previously reported. In
15 the present study, T classification of modified Pittsburgh
16 staging system was also confirmed as prognostic factor by
17 multivariate analysis of all 95 patients. Of note, oncological
18 outcome of the patients with T4 was extremely poor compared with
19 those of patients with T1, T2 and T3. The 5-year OS rate of
20 patients with T4 was 42.9%, while those of patients T1, T2 and
21 T3 were 93.3%, 95.2%, 84.7%, respectively. However, reflecting
22 the recent advances in surgical techniques, surgical navigation
23 system and diagnostic imaging, oncological outcome of
24 SCC-EAC/ME has gradually improved. In 1970s, Lewis reported

1 5-year OS rate of 25% in review of 100 cases.¹⁹⁾ On the other
2 hand, Yin reported 5-year OS rate of 66% in 2006.⁵⁾ In
3 meta-analysis, 5-year OS rates of patients with T3 and T4 were
4 57.5% and 22.9%, respectively in the period of 1976-2008.²⁰⁾
5 Those increased up to 72.5% and 35.8%, respectively in the
6 period of 2006-2013.²¹⁾ In addition, TPF-RT have provided the
7 promising oncological outcome of advanced SCC-EAC/ME including
8 unresectable far advanced cancers.⁸⁾⁻¹⁰⁾ These reports and ours
9 demonstrate the necessity for revising TNM classification.

10 Mazzoni²²⁾ proposed to divide T3 of modified Pittsburgh
11 classification into T3a (tumour extending < 5mm from cartilage
12 to periauricular soft tissues, or tumor strictly limited to the
13 anterior bone wall and growing < 5mm into the parotid space)
14 and T3b (same as for T3a, but extending > 5mm). Also, they divided
15 T4 into T4a (tumour growing into mastoid, without facial nerve
16 paresis) and T4b (tumour growing into mastoid with facial
17 paresis, or infratemporal space, or medial wall of tympanum,
18 labyrinth, petrous bone). Although Mazzoni's classification is
19 useful in case of surgical resection, there were no
20 consideration for resectable and unresectable tumors treated
21 by intensified chemoradiotherapy such as TPF-RT as shown in the
22 present and our previous studies ^{8,9,10)}. To address this
23 limitation, we subclassified T4 disease into two subclasses
24 according to the prognostic factors, brain invasion, internal

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

13 In the present series, treatment period was also found
14 as a significant independent prognostic factor by multivariate
15 analysis. The most possible reason for the improved oncological
16 outcome with time is the change of our treatment policy for
17 non-surgical treatment from CDDP-CRT to TPF-CRT. Advances in
18 imaging and surgical technique supported by surgical navigation
19 might also contribute to the improved survival, as shown in the
20 meta-analysis²¹).

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

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

6 **Conclusion**

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

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14 manuscript.

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1 Tables and Figure

2 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	- -	-	-

3 Abbreviation: LTBR; lateral temporal bone resection, STBR; subtotal
 4 temporal bone resection, CDDP-CRT; chemoradio therapy with Cisplatin,
 5 TPF-CRT; chemoradio therapy with Dosetaxel, 5-FU, and Cisplatin, RT;
 6 Radiotherapy, ND; Neck Dissection

1 **Table 2**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

3

4 **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

1

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

4

5

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	66 (45-70)	60 (44-70)
(Range)		

Abbreviation: RT; radiation therapy, TPF; cisplatin+docetaxel+5-FU,
IMRT; intensity modulated radiation therapy
Proton beam therapy was excluded from RT dose.

1 **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	85	76.0%	0.011
	Auditory Canal			
	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

1 **Table 6 Univariate analysis of T4 patients according to**
 2 **invasion sites**

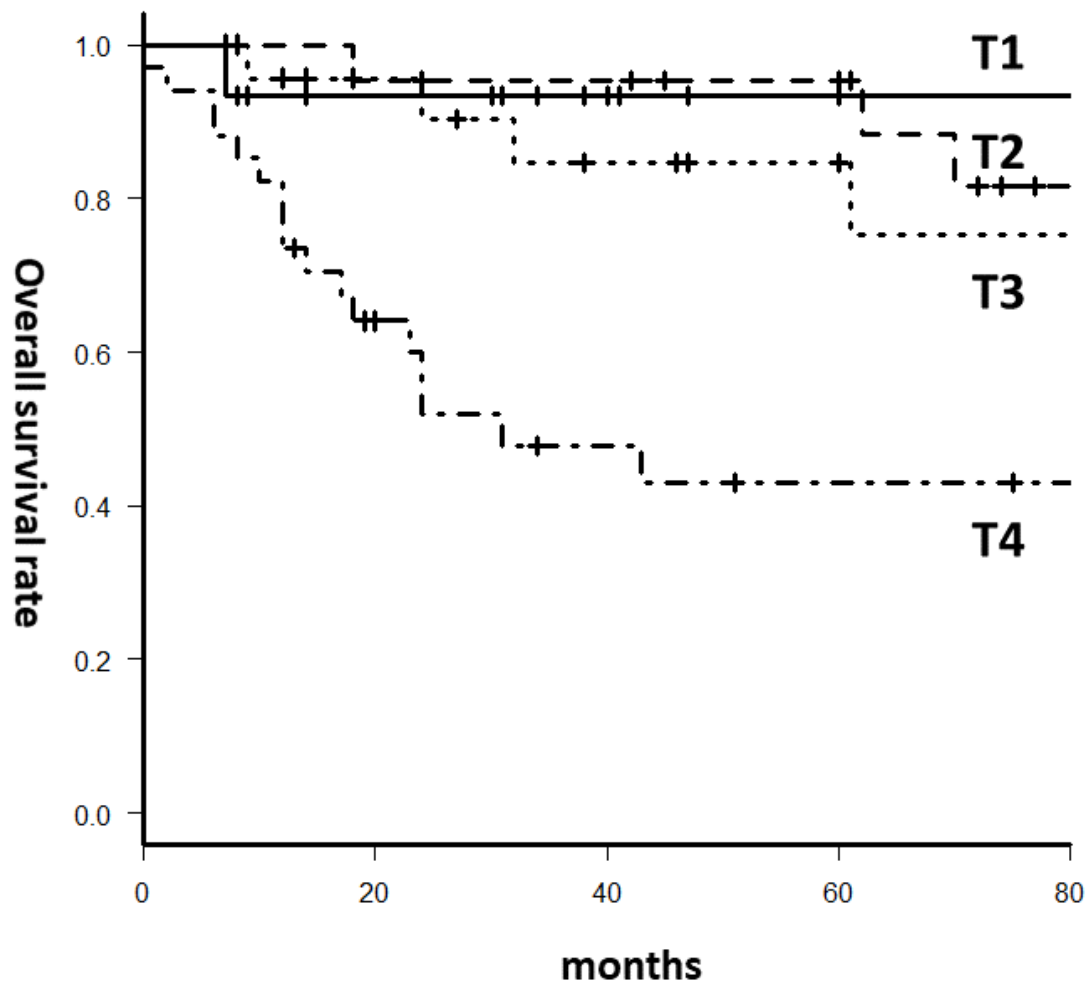
Invasion site		Number	of 5-year OS	P value
		patients		
Brain	+	6	No patient	0.024
	-	28	48.4%	
Internal carotid artery	+	10	20.0%	0.049
	-	24	55.6%	
Internal jugular vein	+	14	16.3%	0.040
	-	20	70.0%	
Dura	+	19	39.7%	0.37
	-	15	48.9%	
Facial nerve	+	9	37.0%	0.84
	-	25	46.0%	
Temporal subcutaneous	+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

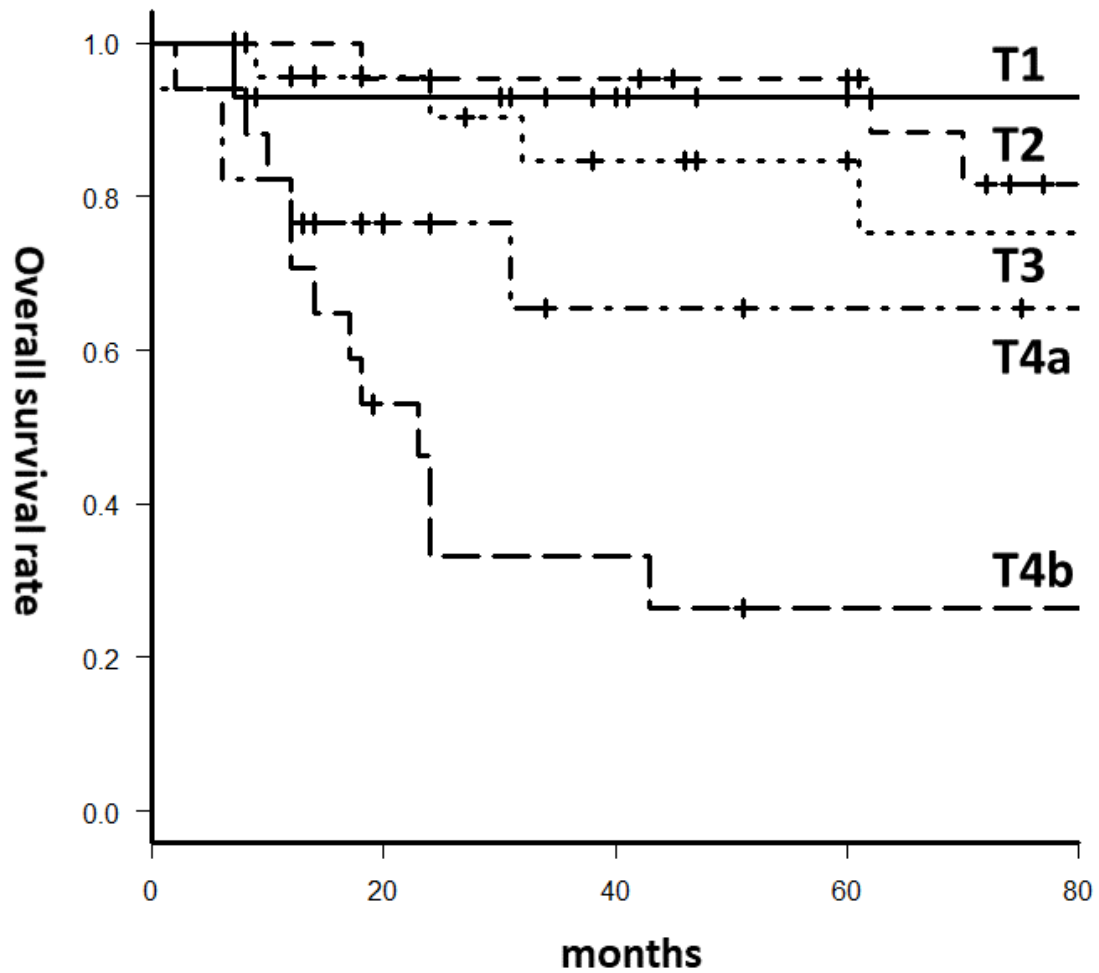
Abbreviations; CRT; chemoradio therapy, RT; radiotherapy

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%, $p=0.049$)

1 **Bullet Point Summary**

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

