Eur J Clin Microbiol Infect Dis (2011) 30:527–532
DOI 10.1007/s10096-010-1114-9

ARTICLE

Precipitating factors in the pathogenesis of peritonsillar abscess and bacteriological significance of the *Streptococcus milleri* group

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Received: 20 August 2010 / Accepted: 27 October 2010 / Published online: 18 November 2010

Abstract Peritonsillar abscess (PTA) is conventionally considered to be a complication of acute tonsillitis, but no pathogenical association has been demonstrated. To investigate the precipitating factors in the pathogenesis of PTA, the clinical status of 117 patients with PTA and 78 patients with peritonsillar cellulitis (PC) were reviewed, comparing them with 188 cases of acute tonsillitis as a control group. The period between the onset of symptoms and the date of starting hospitalized medication was 4 to 5 days in all the three groups, with no significant differences. Higher prevalence of smoking habit was noted in the PTA group (odds ratio, 1.92; 95% confidence interval, 1.17–3.16). Bacteriological culture revealed that 55 of 67 aerobic isolates were *Streptococcus* subspecies, with the *Streptococcus milleri* group (SMG) as the most common (20 isolates). Twenty-three anaerobic species were isolated. Only 51% of the patients with neither the SMG nor anaerobic bacteria were smokers, whereas 90% of the patients with both the SMG and anaerobic bacteria were smokers. We hypothesize that delay or failure to receive medical care do not contribute to the pathogenesis of PTA or PC, and that smoking is positively correlated with the occurrence of PTA, as well as the bacteriological character.

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Introduction

Peritonsillar abscess (PTA) is the most common type of deep neck infection and is associated with significant morbidity and occasional mortality. Progression of PTA leads to further compromise of the pharynx as well as the larynx, resulting in dysphagia, and interference in the airway. PTA is conventionally considered to be a complication of acute tonsillitis or peritonsillar cellulitis (PC) [1]. However, no studies have demonstrated the association between PTA and tonsillitis empirically [2, 3]. Thus, the purpose of this study was to investigate the precipitating factors in the pathogenesis of PTA, focusing on (1) a delay in the treatment, (2) a history of smoking, and (3) the co-existence of the *Streptococcus milleri* group (SMG) with anaerobes. Specifically, we retrospectively reviewed the clinical features of 117 patients with PTA and 78 patients with PC treated in the last 5 years at our department, and 188 patients with acute tonsillitis, who received inpatient care during the same period, as a control group.

A few reports have examined cigarette smoking in patients with PTA [4–6]. However, these studies were comparisons with the prevalence of smoking in the general population. The present study analyzed the prevalence of smoking in our three patient groups.

Streptococcus intermedius, *Streptococcus constellatus*, and *Streptococcus anginosus* are collectively referred to as the SMG [7]. These common inhabitants of the mouth and

gastrointestinal tract can become aggressive and cause abscess formation in the body [8]. Although the SMG was not well recognized as important previously, the co-existence of the SMG with anaerobes may accelerate inflammation [9, 10]. We reviewed cultures obtained from the patients with PTA, and analyzed the relationships between prevalence of smoking and co-existence of SMG with anaerobes.

Materials and methods

Study population

Our 117 patients with PTA and 78 patients with PC were admitted to Iwaki-Kyoritsu General Hospital between August 2002 and July 2007. Iwaki City has a population of 350,000 people, and is located on the northern Pacific Ocean side of Japan. Our hospital is one of only two hospitals in Iwaki City which provide full-time otolaryngological medical care. The other hospitals have only part time otolaryngeal examination programs or private clinics. Thus, almost all patients who should receive ENT hospitalization care are referred to our department from the local district. Patients were routinely interviewed regarding onset of symptoms, smoking habits, and previous medical care before admission to our department. Patients who admitted to smoking more than one cigarette per day on average over the previous year were included in the smoking group.

Differentiation of PTA from PC is sometimes difficult and a common diagnostic problem [2], so the diagnosis of PTA was based not only on the typical clinical signs (swelling of the involved peritonsillar tissues, with bulging of the tonsillar pillars or soft palate), but was verified by the presence of pus at aspiration or incision. In acute tonsillitis, both tonsils become swollen, bright red, and/or coated in acute tonsillitis. These physical findings are clearly different from those of PC. All patients with PTA or PC admitted to our department received inpatient hospital care including systemic administration of antibiotics and hydration. The control group of 188 patients with acute tonsillitis received inpatient care during the study period. Normally, patients with acute tonsillitis receive outpatient medical care in our department. These control patients had severe inflammatory findings on both sides of the tonsils, and could not take nutrition via the mouth.

This study was approved by the ethics committee of Iwaki Kyoritsu General Hospital, and informed consent was obtained from the subjects.

Bacteriological analysis

Cultures were obtained by needle aspiration of the purulent contents or by incisional drainage. The material collected with a syringe or swabs was immediately sealed and generally transported to the laboratory within 15 hours. For aerobic bacteria, sheep blood, chocolate agar plates were incubated at 37°C in 5% CO_2 for 48 hours. For anaerobic bacteria, the specimen material was placed onto prereduced vitamin K10 enriched brucella blood agar, and incubated in GasPac jars for 48 hours. Plates that showed growth were incubated for at least 7 days. Aerobic bacteria were identified with standard methods, and anaerobic bacteria were identified using the API 20 A (Sysmex bioMérieux Co., Ltd., Tokyo, Japan) including Gram staining.

Statistical analysis

The differences in frequencies between groups were statistically examined by the chi-square test or Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with Statview (SAS Inc., Cary, NC, USA) using unconditional logistic regression models to assess the strength of associations between PTA or PC and potential risk factors.

Results

Age and sex distribution

Figure 1 shows the distribution of each patient group by sex and age. The most common age of the patients with PTA was in the 20s, ranging from 6 to 75 years of age. The mean ages were 36.0±14.4 years for the 87 male patients, and 34.9±14.4 years for the 30 female patients. The most common ages of the patients with PC were in the 20s and 40s. The mean age was 38.5±15.0 years for the 57 male patients, and 40.2±20.5 years for the 21 female patients. The most common age of the control patients was in the 20s, which were similar to the PTA group. However, there were fewer patients older than 40 years compared with the PTA group. The mean age was 29.9±8.9 years for the 128 male patients, and 28.7±10.7 years for the 60 female patients, showing that the control group was younger than the PTA and PC groups. The ratios of male to female (2.9 and 2.7, respectively) were slightly higher in the PTA and PC groups compared to the control group (2.1). However, sex was not positively associated with the risk as shown in Table 1.

Period between onset and medical care

The periods between the onset of pharyngeal pain and starting hospitalized medical care were compared. Almost all patients in the PTA group underwent drainage procedures within 2 days of hospitalization. The only exceptions were three patients who underwent drainage 3 or 4 days

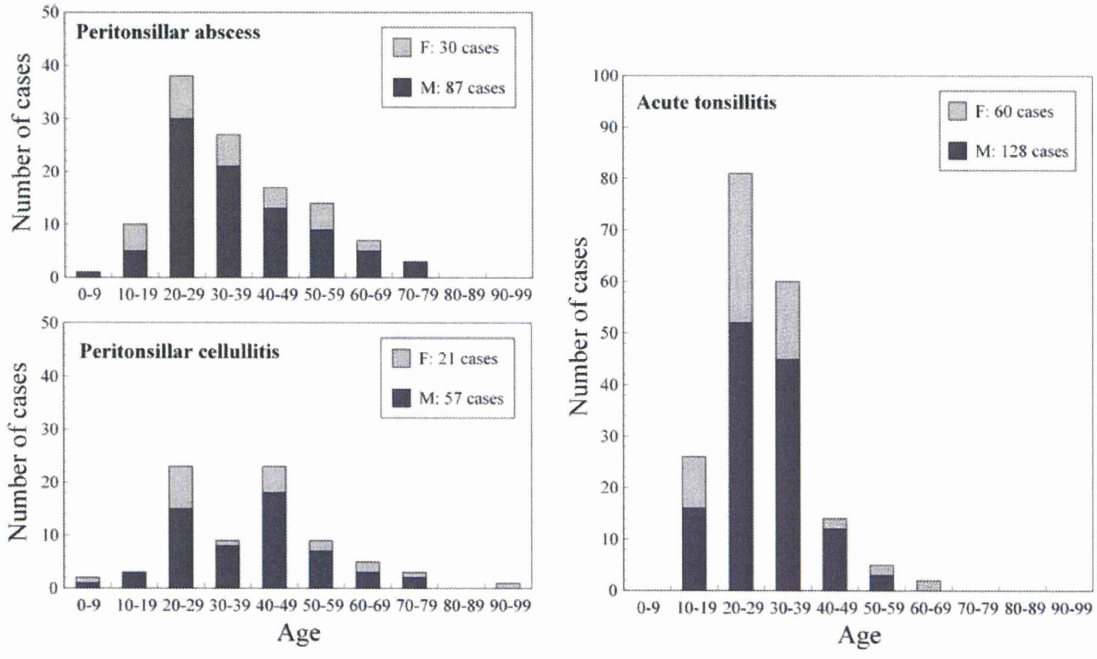

Fig. 1 Age and sex distributions of patients treated for peritonsillar abscess, peritonsillar cellulitis, and acute tonsillitis

after hospitalization. Therefore, the period between onset of pain and hospitalization reflected the period in medical care after the onset of symptoms. The mean period for the PTA, PC, and control groups was 5.4 days, 4.4 days, and 4.5 days, respectively, with no statistical differences (one-way analysis of variance, $F=2.09$).

To further address the hypothesis that failure to receive medical care might result in PTA, analyses were conducted addressing whether patients had received medical care before being admitted to the department (Table 1). In the PTA group, 71 (61%) of 117 patients had received medical care at another clinic, compared to 126 (67%) of 188 patients in the control group. Surprisingly, more patients had received no medical care in the PC group (51%) than in the PTA and control groups.

Comparison of smoking habits

Clinical records about smoking habits were not available in four males and three females of the PTA group, one male of

Table 1 Odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression models for the association between types of disease and sex, previous medication and smoking

Risk factor	Parameter	Peritonsillar abscess	Peritonsillar cellulitis	Acute tonsillitis	*P* for trend
Sex	Female	30 (26%)	21 (27%)	60 (32%)	
	Male	87 (74%)	57 (73%)	128 (68%)	
Male vs. female (reference)	Crude OR (95% CI)	1.36 (0.81–2.28)	1.27(0.71–2.23)	1.00 (referent)	0.22
	Age-adjusted OR (95% CI)	1.33 (0.78–2.25)	1.23 (0.67–2.26)	1.00 (referent)	0.28
Previous medication	Received	71 (61%)	38 (49%)	126 (67%)	
	None	46 (39%)	40 (51%)	62 (33%)	
None vs. received (reference)	Crude OR (95% CI)	1.32 (0.82–2.13)	2.14 (1.25–3.66)	1.00 (referent)	0.17
	Age–sex-adjusted OR (95% CI)	1.25 (0.77–2.05)	2.01 (1.15–3.53)	1.00 (referent)	0.31
Smoking	None	34 (31%)	35 (45%)	86 (46%)	
	Smoker	76 (69%)	42 (55%)	100 (54%)	
Smoker vs. none (reference)	Crude OR (95% CI)	1.92 (1.17–3.16)	1.03 (0.61–1.76)	1.00 (referent)	0.01
	Age–sex-adjusted OR (95% CI)	1.75 (1.02–2.99)	0.90 (0.50–1.61)	1.00 (referent)	0.05

the PC group, and two males of the control group. Smoking habits were reported by 76 (69%) of the remaining 110 patients in the PTA group, 42 (55%) of 77 patients in the PC group, and 100 (54%) of the 186 patients in the control group, as shown in Table 1. The differences between the three groups were statistically significant (chi-square test, $p<0.05$). The crude and age–sex-adjusted ORs for the PTA group were 1.92 (95% CI, 1.17–3.16) and 1.75 (95% CI, 1.02–2.99), respectively. Therefore, a patient with PTA was about two times more likely to report smoking habits compared with a patient suffering from acute tonsillitis.

To further investigate the relationship between smoking and PTA, the numbers of cigarettes smoked per day were analyzed. More than 19 cigarettes per day were smoked by 49% of patients in the PTA group, compared to 31% and 35% in the PC and control groups, respectively. Most female patients smoked less than ten cigarettes per day in all three groups. The risk of PTA was increased among patients smoking ≥20 cigarettes/day compared to patients smoking <20 cigarettes/day (OR, 1.80; 95% CI, 1.11–2.90). With regard to the PC group, the risk of PC was not increased among patients smoking ≥20 cigarettes/day compared to patients smoking <20 cigarettes/day (OR, 0.84; 95% CI, 0.48–1.49). A similar incidence risk was noted for the period of smoking. The incidence risk of PTA was increased among patients smoking for ≥10 years compared to patients smoking for <10 years (OR, 1.86; 95% CI, 1.15–3.01). With regard to the PC group, the incidence risk was not increased among patients smoking for ≥10 years compared to patients smoking for <10 years (OR, 1.01; 95% CI, 0.58–1.75).

Bacteriological analysis

Bacteriological culture tests were performed in 65 of 117 PTA cases. Only aerobic or facultative bacteria were recovered in 38 specimens, only anaerobic bacteria in three, and mixed aerobic and anaerobic bacteria in 17. Cultures showed no growth in seven cases. A total of 90 bacterial isolates and two *Candida* subspecies (spp.) isolates were recovered (1.4 isolates per specimen), as shown in Table 2.

A total of 23 anaerobic species were identified, including *Prevotella* spp. (9 isolates) and *Peptostreptococcus* spp. (8 isolates). A total of 67 aerobic and facultative species were detected, including *Streptococcus* spp. in 55 isolates. SMG were the most common type of *Streptococcus* spp. (20 isolates), consisting of 13 isolates of *S. constellatus* and 7 isolates of *S. intermedius*. None of the 20 cases with positive SMG infection had two or more isolates of the SMG.

Half of the 20 cases with SMG infection also had anaerobic bacteria infection. We thus divided the 65 cases into four groups according to the isolates of the SMG and anaerobes: both SMG and anaerobic isolates, SMG but not anaerobic isolates, anaerobic but not SMG isolates, and neither SMG nor anaerobic isolates. Surprisingly, nine (90%) of the ten patients with both SMG and anaerobic isolates were smokers. On the other hand, 18 (51%) of the 35 patients with neither SMG nor anaerobic isolates were smokers. Significant differences were noted among the four groups in smoking patients (two-tailed Fisher's exact test, $p<0.05$), as shown in Table 3, but not in non-smoker patients, as shown in Table 3.

Discussion

To investigate the precipitating factors in the pathogenesis of PTA, the present retrospective study compared the clinical status of 117 patients with PTA and 78 patients with PC, with 188 patients with acute tonsillitis receiving inpatient hospital medication. The control patients were limited to those suffering from severe tonsillitis. If patients with acute tonsillitis who received outpatient care had been included in the control group, greater differences from the PTA and PC groups might be expected. The only factor that might be overestimated is the delay or failure of previous medicine, whereas our preliminary analysis did not find any significant differences in this period. Therefore, our control group probably did not lead to overestimation of differences in the clinical status of the PTA or PC group from the acute tonsillitis control group.

The symptomatology of sore throat has been reported to begin only 3 to 5 days from the onset of PTA [1, 6]. If PTA develops secondary to acute tonsillitis, delay or failure to receive medical care will lead to the development of PTA. However, the PTA, PC, and acute tonsillitis control groups showed no significant differences in the period between the onset of pharyngeal pain and the date of starting hospitalized medical care. Also, the prevalence of previous medication in the PTA group was almost the same as in the control group. These findings suggest that delay in starting to receive medical care or failure to receive medication do not contribute to the development of PTA. Interestingly, the PC group showed higher prevalence of no previous medication, presumably because the attending physicians, who were mostly expecting ENT problems, recognized the risks of PC and immediately referred the patients to our department without starting treatment.

Cigarette smoking is related to a wide variety of still poorly known toxic mechanisms leading to oxidative injury. A clinicopathological study of the palatine tonsil found that smoking induces problems with adequate immune response, increasing incidence of pharyngotonsillar infections [11]. Since the link between smoking and

Table 2 Culture results of peritonsillar abscess (PTA) patients

Anaerobic isolates	Number of isolates	Aerobic and facultative isolates	Number of isolates
Prevottela spp.	9	*Sterptococcus milleri* group	20
Peptostreptococcus spp.	8	*Streptococcus pyogenes*	9
Fusobactrrium spp.	3	*Streptococcus mitis*	9
Bacteroideus spp.	1	Other *Streptococcus* spp.	17
Other species	2	Other species	12
Total	23		67

quinsy was first suggested [4], only a few of studies have investigated the relationship of smoking with PTA. These studies found that the prevalence of smoking was higher than that of the general population [5, 6]. Our study was stronger than previous studies examining the association between smoking and risk of PTA because the prevalence of smoking habit was compared not only with the general population, but also with patients with acute tonsillitis; and the number of cigarettes per day and period of smoking were also analyzed.

The smoking rates in the Japanese general male and female populations are 39.9% and 10%, respectively, derived from the survey by the Ministry of Health, Labour and Welfare of Japan [12]. The prevalence of smoking in the male patients in the PTA, PC, and control groups were 83% (69/83), 66% (37/56), and 61% (77/126), respectively. In all three groups, ratios of smokers among male patients were higher than in the general male population. The prevalence of smoking in the female patients in the PTA, PC, and control groups were 26% (7/27), 24% (5/21), and 38% (23/60), respectively. In all three groups, ratios of smokers among female patients were also higher than in the general female population [12].

We found significant prevalence of smoking habits in patients with PTA (69%) compared with those with acute tonsillitis (54%) (Table 1), higher than previously reported [5]. This previous study defined patients in the PTA group as those who received abscess tonsillectomy, which might include patients with PC, whereas we defined the PTA group by the presence of pus detected by aspiration or incision. Combining the PTA and PC groups gave a prevalence of smoking of 63%, similar to the previous report [5]. The PTA group also had a significantly higher prevalence of smoking ≥20 cigarettes/day, and significantly longer smoking history, which are consistent with previous findings that a longer history along with greater daily number of cigarettes smoked are clearly correlated with both recurrent infections and histological changes [11, 13].

Table 3 Association between the existence of anaerobic and *Streptococcus milleri* group (SMG)

Category	Anaerobic (+)	Anaerobic (-)
Smokers[a]		
SMG (+)	9	7
SMG (-)	5	18
Non-smokers[b]		
SMG (+)	1	3
SMG (-)	5	17

[a] Fisher's exact test: $P<0.05$

[b] Fisher's exact test: $P>0.999$

Our bacteriological survey of 65 PTA cases isolated 23 anaerobic microorganisms. Only four isolates contained only anaerobic bacteria, and the others yielded mixed aerobic and anaerobic species. These results are consistent with previous reports showing the polymicrobial nature and importance of anaerobic bacteria in PTA [14, 15]. Meticulous anaerobic culture technique showed that anaerobes were present in all PTA cases, with only anaerobes in 19%, and aspiration methods rather than swabs were recommended [14]. In our study, aspiration failed to collect pus in some patients, so specimens were collected by swabs followed by incisional drainage. These factors might be responsible for the relatively low rates of isolation of anaerobes (31%) and positive cultures (1.4 isolates per specimen). Despite these issues, our bacteriological analyses revealed some interesting findings. The SMG was the most frequent isolate (31% of cases), which is recently recognized as an important cause of pyogenic infection and head and neck abscess [8, 16, 17]. Fifteen of the 20 patients with positive SMG were males, consistent with previous reports showing a higher incidence of infections among males [8, 18].

The detailed pathogenesis of the SMG remains unclear, but mucous infection by normal flora is thought to occur due to an imbalance between the organisms and host immunodefense in the deep neck abscess, including our previous report [9, 17]. Our bacteriological analyses showed that patients with mixed infection of anaerobes and the SMG had significantly higher smoking prevalence (90%) than the other patients. Moreover, patients with positive SMG and negative anaerobic isolation revealed higher smoking prevalence (70%) than those with negative SMG and positive anaerobic isolation (55.6%). These findings indicate that cigarette smoking is correlated with infection of pathogens which accelerate abscess formation.

Other than smoking, a few variables are associated with PTA. One aspect of pathogenesis may involve Weber's gland in the supratonsillar space, which acts to clean debris on the tonsillar crypts, and could easily develop infections leading to cellulitis or abscess into the supratonsillar space [1]. Another aspect of pathogenesis is based on the similar bacteriological and epidemiological association between periodontitis and PTA [19, 20].Approximately 20% of 84 patients with PTA were reported to have significant dental caries and allergies [19]. Since our study did not examine the role of periodontitis as an independent variable, further studies are necessary to explore whether treatment of periodontal disease could also have a prophylactic effect against PTA. Moreover, self report of smoking may be unreliable, and objective test for smoking may have resulted in a different smoking rate. More study including the measurement of blood cotinine levels would be helpful to overcome these limitations in accurately assessing smoking habit.

Acknowledgements We thank Dr Hideaki Suzuki (Department of Otolaryngology, University of Occupational and Environmental Health) for his comments on the earlier version of this manuscript.

Conflicts of interest We declare that we have no conflict of interest.

Funding None

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Eur Arch Otorhinolaryngol (2011) 268:823–827
DOI 10.1007/s00405-010-1467-9

OTOLOGY

Effects of neck muscle vibration on subjective visual vertical: comparative analysis with effects on nystagmus

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Received: 7 September 2010 / Accepted: 9 December 2010 / Published online: 23 December 2010

Abstract In patients with unilateral vestibular dysfunction, vibratory stimulation to the neck muscles not only induces shift of the subjective visual vertical (SVV), but also enhances the generation of nystagmus. In the present study, the effects of neck vibration on the SVV were compared with those on nystagmus in patients with unilateral vestibular schwannoma (14 patients; 6 males and 8 females, mean age 54.2 years). The results indicated that the presence of nystagmus and magnitude of the SVV were generally correlated, neck vibration significantly increased the abnormal shift of the SVV and the presence of nystagmus, and the effects of vibration to the ipsilateral dorsal neck were significantly larger than those to the contralateral dorsal neck on the SVV, whereas no significant difference was observed in slow phase velocity of nystagmus. The present study suggests that both SVV and nystagmus induced by vibration have many similar clinical features and may be important in assessing the unilateral vestibular dysfunction.

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Keywords Subjective visual vertical · Neck muscles vibration · Nystagmus

Introduction

Human subjects can align the subjective visual vertical (SVV) to within 2–3° of the gravitational vertical [1–4]. This subjective directional sensation is believed to be significantly related to the vestibular otolith function, and is shifted to the ipsilateral side to the lesion in patients with unilateral vestibular dysfunction [1–7]. This pathological shift of the SVV is largest during the acute phase of vestibular dysfunction and is reduced by the vestibular compensation process [6, 7]. Detection of such pathological shift of SVV may be based on vibration of the neck or mastoid area, which is known to increase the pathological SVV shift, and is useful to detect unilateral vestibular deficit [4]. On the other hand, neck vibration also induces nystagmus in patients with unilateral vestibular dysfunction, of which the slow phase is directed to the lesion side [8–11]. However, the relationship between the vibration-induced SVV shift and vibration-induced nystagmus is not fully clarified.

The present study compared the effects of neck vibration on the SVV with those on nystagmus in patients with unilateral vestibular schwannoma, examined on the same day.

Materials and methods

This study included 14 patients with vestibular schwannoma, 6 males and 8 females aged 31–73 years (mean 54.2 years), who underwent assessment of the effects of

vibration on the SVV and nystagmus on the same day. Seven patients underwent tumor removal via a translabyrinthine approach (six patients) or a retrosigmoid approach (one patient). Three of these seven patients were examined before and after surgery (translabyrinthine approach), and four patients were only examined after surgery (translabyrinthine approach, three patients; retrosigmoid approach, one patient). The average duration between operation and postoperative examination was 8.9 week (2–32 weeks). On the other hand, seven patients had not undergone surgery at the time of examination.

The SVV was measured using custom-built equipment (Nagashima Medical Instruments Co., Ltd., Tokyo, Japan), which corrects the visual vertical automatically at the beginning of the measurement, based on a built-in level. The patient was presented with a light emission diode (LED) bar (130-mm length, 1-mm width) mounted on a monitor board, which was easily rotated in a clockwise or counterclockwise direction using manipulation buttons, and the angle of the bar could be measured at 0.1° interval (Fig. 1). The vibration source was a commercially available, handheld massager (YCM-8; Yamazen, Higashiosaka, Japan) oscillating at 110 Hz. Vibration was applied to the (right and left) dorsal neck muscle area approximately 3–4 cm below the occipital skull.

The SVV was assessed in the sitting position 0.9 m away from the monitor in a dark room, with the head and chin of the patient fixed with a retainer device. The SVV was measured under the following three different conditions: no vibration, and vibration to the right dorsal neck and to the left dorsal neck. Each measurement condition was tested four times successively, and the average value was calculated. At the beginning of the measurements, the initial position of the bar was set alternately in the clockwise and counterclockwise directions, and the patients were asked to align the LED bar along the axis of the SVV. In the present study, the normal range of the SVV was defined as ±3° from the gravitational vertical, based on previous SVV measurements [4].

Spontaneous nystagmus, as well as nystagmus induced by vibration at the right and left dorsal neck, was observed using infrared goggles. If nystagmus was observed under any condition, spontaneous as well as vibration-induced nystagmus was recorded using electronystagmography (ENG), and the slow phase velocity (SPV) of the horizontal component of the nystagmus was assessed. Nystagmus was recorded for about 30 s for each condition and the maximum SPV was calculated.

All parts of the present study were performed in accordance with the guidelines of the Declaration of Helsinki.

Results

Representative SVV and ENG recordings of nystagmus obtained from a female patient with left vestibular schwannoma are presented in Fig. 2. Her tumor was totally removed through the translabyrinthine approach 8 months previously. No apparent nystagmus was observed without neck vibration, but nystagmus directed to the right side was induced by vibration to both the right and left dorsal neck (Fig. 2 left column). Maximum SPV induced by vibration to the left (ipsilateral to the lesion) and the right (contralateral to the lesion) neck was 7.52 and 7.21°/s, respectively. SVV without vibration and with vibration to the left (ipsilateral) and right (contralateral) neck was 2.025°, 4.35° and 3.125°, respectively, indicating that the SVV was slightly shifted to the left (ipsilateral) side without vibration, and was shifted further to the left side by neck vibration. Therefore, the SVV shift was greater if vibration was applied to the ipsilateral neck as previously reported [4]. The shift of the SVV and the SPV of nystagmus were directed to the ipsilateral side in most patients. Therefore,

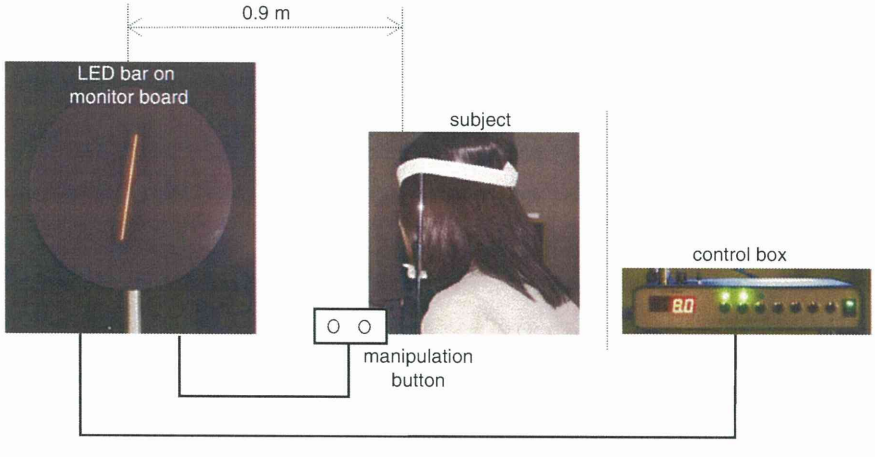

Fig. 1 Schema of SVV measurement. SVV was measured using custom-built equipment (Nagashima Medical Instruments Co., Ltd., Tokyo, Japan) positioned 0.9 m away from a subject. Subjects were asked to adjust the LED bar (130-mm length, 1-mm width) along the axis of the subjective vertical (see text for further details)

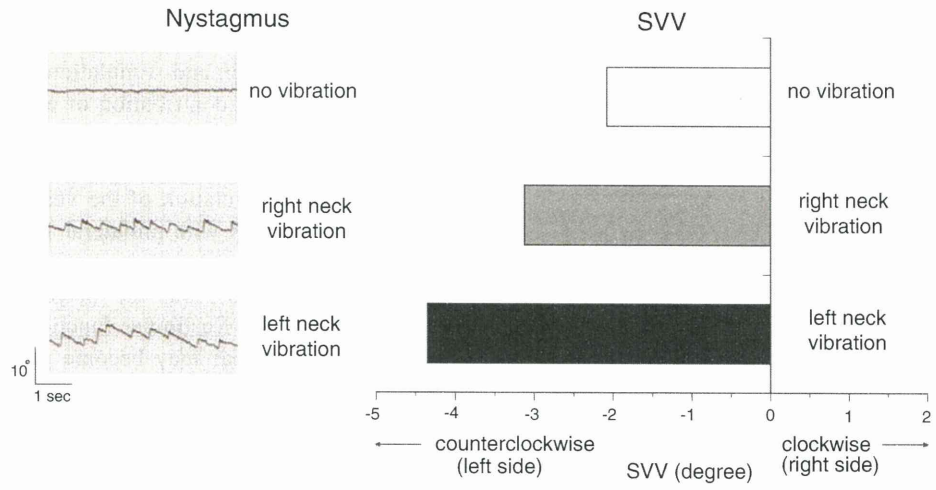

Fig. 2 Typical examples of SVV and ENG recordings of nystagmus obtained from a patient after surgery for left vestibular schwannoma (62 years old, female). ENG recording without vibration, with vibration of the right dorsal neck and with vibration of the left dorsal neck are shown in the *left column*. Vibration of the right and left dorsal neck caused apparent nystagmus directed to the right (intact) side. SVV values without vibration, with vibration of the right dorsal neck and with vibration of the left dorsal neck are presented in the *right column*. SVV was slightly shifted to the left (pathological) side without vibration, and was shifted more to the left side by neck vibration

in the following analysis, the direction of SVV and SPV of nystagmus were given positive and negative values to indicate the ipsilateral and contralateral sides of the lesion, respectively.

The relationship between the SVV value and SPV of the nystagmus is presented in Fig. 3. Nystagmus occurred in 79% of cases of conditions with the SVV shifted by more than 3° from the gravitational vertical, and in only 22% of cases with shift of the SVV within 3°. Figure 3 indicates a significant link between SVV and SPV of the nystagmus ($r = 0.452$, $P < 0.01$). However, analysis of the correlation in the selected cases with nystagmus found no correlation between SPV and SVV. The shift of the SVV and the SPV of the nystagmus were directed to the ipsilateral side of the lesion, except in one preoperative patient in whom the SVV shifted to the contralateral side by more than 3° without nystagmus.

Figure 4 compares the positive rate of abnormal SVV (SVV shifted by more than 3° from the gravitational vertical) with the presence of nystagmus. The positive rates of abnormal SVV and the presence of nystagmus under the three different conditions (no vibration, ipsilateral vibration and contralateral vibration) were very similar (no significant differences). Both significantly increased from about 20 to 60% with vibration ($P < 0.05$).

Figure 5 shows the effects of neck vibration on the SVV and SPV of nystagmus. Mean shift of SVV and mean SPV of nystagmus were significantly increased by neck vibration ($P < 0.05$), with significantly larger effects on the ipsilateral compared to the

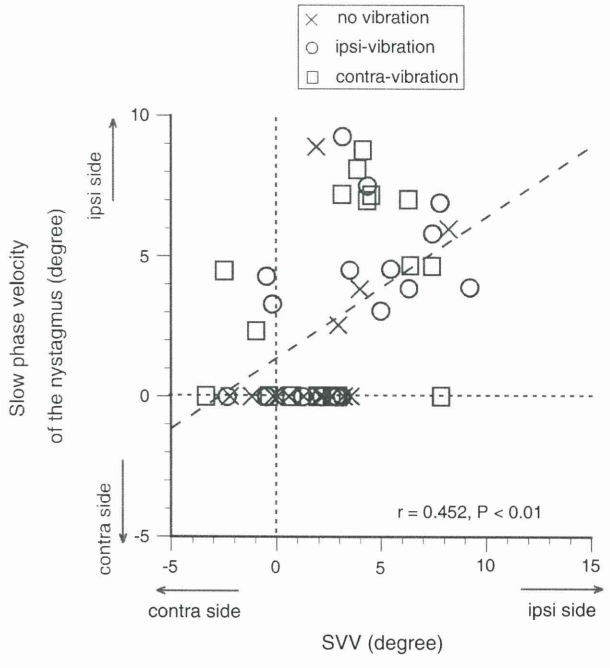

Fig. 3 Relationship between magnitude of SVV and maximum SPV of nystagmus. The magnitude of SPV of the nystagmus was plotted as a function of shifts of SVV. The directions of SVV and nystagmus were determined based on the pathological side (positive and negative values indicate that shift of SVV and SPV of nystagmus were directed to the ipsilateral and contralateral sides of the lesion, respectively) (see text for further details)

contralateral side for SVV ($P < 0.05$), but no significant difference between the ipsilateral and contralateral sides for SPV.

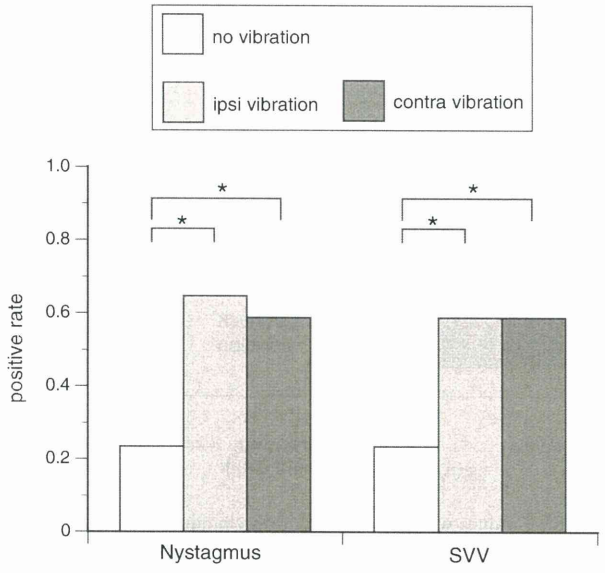

Fig. 4 Increased detectability of SVV and nystagmus by neck vibration. The positive rate of abnormal SVV (SVV shifted more than 3° from the gravitational vertical) and nystagmus was divided into three different conditions (no vibration, and ipsilateral and contralateral neck vibration). *Asterisks* in the figure indicate significant differences ($P < 0.05$ by Chi square test). The positive rates of abnormal SVV and nystagmus are very similar (no significant differences)

Discussion

The present study of the relationship between pathological shift of the SVV and SPV of nystagmus, and the effects of neck vibration in patients with unilateral vestibular schwannoma found that the presence of nystagmus and magnitude of the SVV were correlated, neck vibration significantly increased the abnormal shift of the SVV and the presence of nystagmus, and the effects of vibration to the ipsilateral dorsal neck were significantly larger than those to the contralateral dorsal neck on the SVV, whereas no significant difference was observed in SPV of the nystagmus.

The effects of vibration on the vestibular system may involve the following two mechanisms: direct stimulation of the vestibular organ and stimulation of muscle spindle afferents. The actual contribution of each mechanism to the generation of vibration-induced nystagmus and SVV shift is controversial [4, 9, 12–14]. However, the contribution of direct stimulation of the vestibular organ may be greater in patients with unilateral vestibular dysfunction. Vibration of the dorsal neck could affect bilateral vestibular end organs, but the actual activation level might depend on the vestibular function, as the stimulation of the normal ear may become predominant. As a result, the shift of the SVV and the SPV of the evoked nystagmus tend to be directed to the lesion side, regardless of the side of stimulation.

Vibration is known to cause the SVV to shift to the stimulated side in normal subjects, and the stimulation of muscle spindle afferents may be mainly responsible for this phenomenon [4, 7, 12, 15]. Thus, if SVV shift reflects the summed effects of direct stimulation of the vestibular organ and neck muscle spindle, the predominant effect of ipsilateral stimulation on the SVV, as seen in the present as well as several previous studies [4, 12, 13], may be explained as ipsilateral shift of SVV caused by vestibular unbalance that is enhanced by ipsilateral neck stimulation, but diminished by contralateral neck vibration. In contrast, such differences with the side of neck vibration were not observed in nystagmus in patients with unilateral vestibular dysfunction [9, 11]. Why such differences cannot be observed in nystagmus, but are observed in the SVV, remains unclear, although the relative magnitude of vibration effects via muscle spindle afferents and direct stimulation of the vestibular end organ might be different.

The present study indicates that both SVV and nystagmus affected by neck vibration have many similar clinical features, and may be important in assessing unilateral vestibular dysfunction.

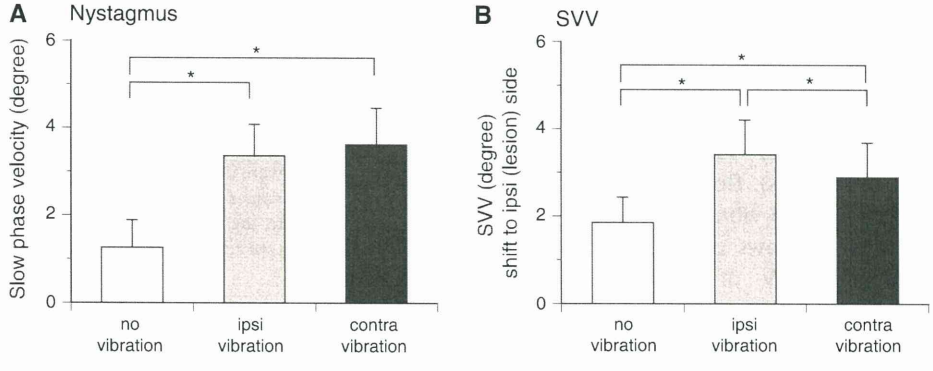

Fig. 5 Effects of neck vibration on the magnitude of SVV and SPV of nystagmus. *Asterisks* in the figure indicate significant differences ($P < 0.05$ by paired t test) (see text for further details)

Tohoku J. Exp. Med., 2011, **223**, 17-25

Surgical Treatment Is Recommended for Advanced Oral Squamous Cell Carcinoma

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Oral squamous cell carcinoma is one of the most frequent types of head and neck cancers in Japan. Although recent reports have shown positive results of non-surgical treatment for advanced head and neck squamous cell carcinoma, including tongue cancer, no clear treatment strategies have been established for oral cancers, except for tongue cancer. To assess appropriate therapies, we conducted a retrospective chart review of 114 Japanese patients with oral cancers that were pathologically diagnosed as squamous cell carcinoma, excluding tongue cancers. The overall and the disease specific 5-year survival rates were 53% and 61%, respectively. Univariate and multivariate analyses revealed a lower stage (I, II, or III) and non-surgical treatment as good and poor prognostic factors of oral squamous cell carcinoma, respectively, based on their hazard ratios of 0.17 (95% CI 0.045-0.60, $p = 0.0061$) and 5.3 (95% CI 2.7-11, $p < 0.0001$). Furthermore, impact of surgery was well documented in the operable stage IVa cancers ($p = 0.00015$). The surgical treatment consisted of the wide resection of the primary tumor and the neck dissection for stage III or IV tumors. The present data also suggest that adjunctive therapy, such as post-operative radiation therapy or post-operative chemo-radiation therapy, shows no survival benefit compared to the surgery alone. We therefore recommend the surgical treatment for advanced oral squamous cell carcinoma in Japanese patients. These results would be helpful in future clinical trials, especially in non-surgical treatment studies of oral squamous cell carcinoma in Japan.

Keywords: oral cancer; buccal mucosa; gingiva; oral floor; hard palate
Tohoku J. Exp. Med., 2011, **223** (1), 17-25.

In Japan, oral cancer is one of the most frequent types of head and neck cancers (Matsuda et al. 2009). We have previously reported on prognostic factors and treatment strategies for tongue squamous cell carcinoma (tongue SCC) that is the most common type of oral cancers (Tateda et al. 2000; Shiga et al. 2007).

Recent research revealed that chemo-radiation therapy (CRT) seems to be effective for advanced head and neck squamous cell carcinomas (head and neck SCC) including oral squamous cell carcinomas (oral SCC) (Robbins et al. 2005; Doweck et al. 2008; Fuwa et al. 2008; Stenson et al. 2010). However, the treatment strategies have not yet been established for oral SCC, excluding tongue SCC, such as SCC in buccal mucosa, gingiva, hard palate and oral floor, because of the rare incidence (Ariyoshi et al. 2008). Actually, major clinical studies about CRT for oral SCC included a large number of tongue SCC and a small number of other oral SCC. Referring to previous reports regarding poor prognostic factors for oral SCC excluding tongue SCC (Soo et al. 1988; Fang et al. 1997; Dias et al. 2003), T4a and N2b in accordance with the guidelines of the Union Internationale Contre le Cancer (UICC) 2002 have been considered to be prognostic factors; however, the available data are still insufficient to draw any significant conclusions or select the optimal treatments for oral SCC.

We herein report a retrospective analysis of the treatment outcomes of patients with oral SCC other than tongue SCC to develop appropriate treatment strategies at every stage. This study was performed at two facilities that have the same treatment policy, basically consisting of a wide resection or intensive CRT.

Subjects and Methods

The subjects included 114 patients with oral SCC (excluding tongue SCC) who received inpatient treatment at the Department of Otolaryngology-Head and Neck Surgery of the Tohoku University School of Medicine and the Division of Head and Neck Surgery of the Miyagi Cancer Center between January 1993 and December 2004.

Received March 11, 2010; revision accepted for publication December 3, 2010. doi: 10.1620/tjem.223.17
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Institutional review board approval was obtained for this study, and written informed consent was obtained from all patients. Before treatment, staging was conducted for all patients using tumor biopsy, head and neck CT, head and neck MRI, thoracoabdominal CT, bone scintigram, etc. In the diagnosis of cervical lymph node metastases with CT and MRI, submandibular lymphadenopathy of 15 mm or more, those in other sites of 10 mm or more, and those with central necrosis were considered positive. Staging was conducted in accordance with the guidelines of the UICC 2002. Follow-up periods were calculated from the day when the initial treatment had been started. The median follow-up period was 44 months (range 1-146 months), and the follow-up period of all surviving patients was 20 months or more. All follow-up data were updated at the end of October 2008.

In the classification by sites, hard palate SCC and upper gingival SCC were analyzed in combination due to the anatomical continuity and the small number of patients. The treatment policy at both of these facilities was basically surgery. Regarding the postoperative adjunctive treatment, post-operative radiation therapy (PORT) or post-operative chemo-radiation therapy (POCRT) for patients with cancer-positive stumps, multiple cervical lymph node metastases and extracapsular progression of lymph node metastasis were performed unless the patients rejected them. The surgical treatment basically consisted of a wide resection of the primary tumor and a neck dissection for stage III or IV tumors. In addition, for patients, in whom surgery could not be performed due to patient refusal, definitive treatment, mainly with definitive RT or CRT (RT/CRT) was thus conducted. Furthermore, RT/CRT was basically conducted for inoperative patients with T4b, M1 or other prominent disorders including multiple primary cancers. Those patients received the standard fractionated radiation therapy given at a dosage of 4-MV X-rays of 2 Gray (Gy) per fraction, 5 fractions per week.

Regarding the CRT regimen, platinum agents, such as cisplatin (CDDP), and/or fluorouracil (5FU) were concomitantly administered to the patients. Only one patient received docetaxel additionally. Our standard regimen of CRT is as follows: iaCDDP, intra-arterial infusion of high dose CDDP (100-150 mg/m^2 weekly, 4-6 times); CF, systematic infusion of CDDP (70 mg/m^2 day 2) and 5FU (1,000 mg/body day 1-5) every four weeks, 2 times; ivCDDP, systematic infusion of CDDP (50 mg/m^2) weekly, 4-6 times; and DCF, systematic infusion of combined CDDP (60 mg/m^2 day2), 5FU (1,000 mg/body day 1-5) and docetaxel (50 mg/m^2 day 2) every four weeks, 2 times.

The patients were analyzed for gender, age, TNM classification, stage, site and initial therapeutic regimen, recurrence, period before recurrence and survival. Survival rates were calculated using the Kaplan-Meier method, and significant differences were analyzed with the log-rank test. Univariate and multivariate analyses were conducted using the Cox proportional-hazards model. For the analyses, Stat View version 5.0 for Windows (SAS Institute Inc, Cary, NC) was used. The statistically significant level was 0.05.

Results

Clinical features of the patients with oral SCC

The patients included 85 males and 29 females, aged from 40 to 89 years (median age: 69 years). In the T classification, T4 cancers accounted for 43% of the patients, and in the N classification, lymph node metastases accounted for 50% and N2 patients for 31%. In the classification by stage, advanced cancer (stage III or IV) accounted for 68% of the patients, of which stage IV cancer accounted for 55%. In the classification by site, the buccal mucosa was the most common site and was involved in 37 patients, followed by the oral floor in 35 patients, the lower gingiva in 28 patients, and the upper gingival or hard palate in 14 patients. For the initial therapeutic regimen, 92 patients (81%) underwent treatment including surgery, and 22 (19%) patients did not undergo surgery. The reasons for performing non-surgical treatment were due to simple rejection (4 patients), organ preservation (4 patients), advanced age (4 patients), inoperable stage (T4b or M1) (5 patients), and other disorders including multiple primary cancers (5 patients). Adjunctive therapy for the surgical treatment included PORT for 22 patients, POCRT for 1 patient, and pre-operative or post-operative chemotherapy (6 patients). The reason why POCRT was chosen was due to the fact that the patient had synchronous multiple primary cancers, *i.e.*, advanced cancer of oral floor and esophageal cancer. He was treated with POCRT for oral cancer and with definitive CRT for esophageal cancer. On the other hand, the choices of adjunctive chemotherapy were due to neo-adjuvant chemotherapy prior to surgery in 3 patients, distant metastasis found before surgery in 1 patient and adjunctive chemotherapy protocol until 1998 in 2 patients. The post-operative radiation dose ranged from 46 to 70 Gy (median: 50 Gy) in the patients treated.

Survival analysis

Regarding the survival analysis using the Kaplan-Meier method, the 3-year and 5-year overall survival rates were 59% and 53%, respectively. The 3-year and 5-year disease-specific survival rates were 65% and 61%, respectively.

When the 5-year disease-specific survival rate was analyzed by factor, patients with T4a (43%) or T4b (0%) showed significantly poor prognoses in the T factors, and patients with N2b (48%) or N2c (19%) showed significantly poor prognoses in the N factors (Table 1). In addition, according to stage, stage IV cancers, which accounted for the majority of the patients, had poor prognoses (Fig. 1). In the classification by site, patients with buccal mucosal cancer (47%) tended to show poor prognoses, but no statistical significance was observed (Table 1). In the classification by the initial therapeutic regimen, 92 patients, in whom the treatment was mainly surgery, had a 5-year disease-specific survival rate of 71%, while the 5-year disease-specific survival rate of 22 other patients with non-surgical treatment was 20%, indicating a significantly poor prognosis of non-surgical treatment ($p < 0.0001$) (Fig. 2A).

Regarding adjunctive therapy in combination with the surgical treatment, the 5-year disease-specific survival rates of surgery alone ($n = 63$), PORT ($n = 22$), POCRT ($n = 1$) and pre-operative or post-operative chemotherapy ($n = 6$) were 77%, 53%, 0% and 75%, respectively. Furthermore, when only stage IV patients were examined, these rates of surgery alone ($n = 25$), PORT ($n = 18$) and pre-operative or

Table 1. Disease-specific survival rates according to patient profiles and tumor characteristics.

Factors	Category	No. of Patients	5-year survival (%)	*p* value
Gender	<1> Male	85	58	$p = 0.54$
	<2> Female	29	68	
Age	<1> ≤ 65	45	57	$p = 0.94$
	<2> > 65	69	63	
T	<1> T1	13	77	2 vs 4 $p = 0.0013$
	<2> T2	39	78	1 vs 5 $p = 0.00012$
	<3> T3	13	67	2 vs 5 $p < 0.00001$
	<4> T4a	46	43	3 vs 5 $p = 0.0056$
	<5> T4b	3	0	4 vs 5 $p = 0.015$
N	<1> N0	57	80	1 vs 2 $p = 0.032$
	<2> N1	21	54	1 vs 3 $p = 0.028$
	<3> N2a	4	25	1 vs 4 $p = 0.019$
	<4> N2b	20	48	1 vs 5 $p < 0.00001$
	<5> N2c	12	19	
Stage	<1> I	9	100	1 vs 4 $p = 0.011$
	<2> II	27	84	1 vs 5 $p = 0.00019$
	<3> III	15	79	1 vs 6 $p = 0.0025$
	<4> IVa	56	43	2 vs 4 $p = 0.0023$
	<5> IVb	3	0	2 vs 5 $p < 0.00001$
	<6> IVc	4	-	2 vs 6 $p = 0.00027$
				3 vs 4 $p = 0.043$
				3 vs 5 $p = 0.0013$
				3 vs 6 $p = 0.010$
				4 vs 5 $p = 0.0015$
Site	<1> Buccal mucosa	37	47	1 vs 3 $p = 0.19$
	<2> Oral floor	35	68	
	<3> Lower gingiva	28	69	
	<4> Upper gingiva Hard palate	14	57	
Treatment	<1> Ope	92	71	1 vs 2 $p < 0.00001$
	<1>_1 Ope only	63	77	
	<1>_2 PORT	22	53	
	<1>_3 POCRT	1	0	
	<1>_4 Ope+chemo	6	75	
	<2> RT/CRT	22	20	

Ope, Surgery. RT/CRT, Radiation therapy or chemo-radiation therapy.

post-operative chemotherapy ($n = 5$) were 51%, 47% and 75%, respectively. These data of adjunctive therapy have shown no survival benefit compared to surgery alone. In the analysis of significant differences with the log-rank method, the 4 items of T factors, N factors, stages, and initial therapeutic regimens showed statistically significant differences (Table 1).

Univariate analysis

The results of univariate analysis of the disease-specific survival rates are shown in Table 2. Based on the number of patients and the results of the log-rank method, the parameters to be examined included gender (M vs F), age (≤ 65 vs > 65), T (1, 2 or 3 vs 4), N (0 or 1 vs 2), stage (I, II or III vs IV), site (buccal mucosa vs other sites), and treatment method (RT/CRT vs surgery (OPE)). The 4 items of T, N, stage and treatment method showed statistically significant differences in the disease-specific survival rates, and the hazard ratios were 0.32 ($p = 0.0003$), 0.37 ($p = 0.0013$), 0.20 ($p < 0.0001$), and 4.4 ($p < 0.0001$), respectively.

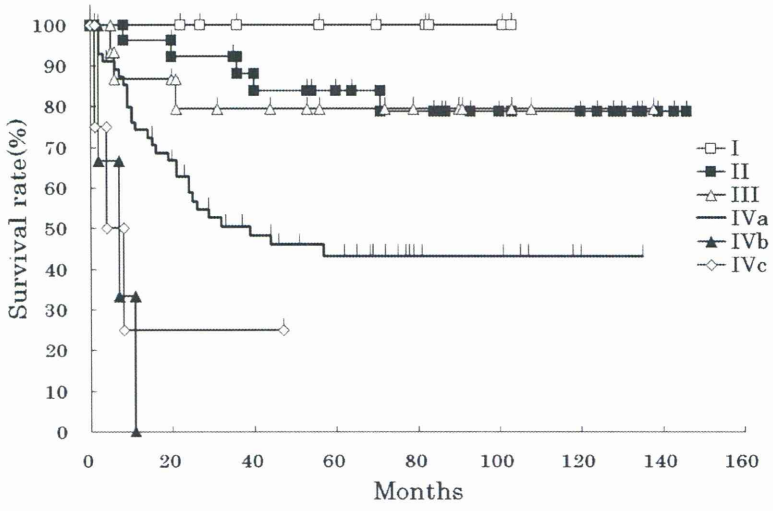

Fig. 1. Disease-specific survival rates by stage.
There was a statistically significant difference as shown in Table 1.

Table 2. Univariate analysis of disease-specific survival rates (Cox proportional-hazards model).

Factors	Category	Hazard ratio	95% CI	*p* value
Gender	M vs F	0.80	0.40 - 1.6	$p = 0.54$
Age	≤ 65 vs > 65	0.98	0.53 - 1.8	$p = 0.94$
T	1 or 2 or 3 vs 4	0.32	0.17 - 0.59	$p = 0.0003$
N	0 or 1 vs 2	0.37	0.21 - 0.68	$p = 0.0013$
Stage	I or II or III vs IV	0.20	0.091 - 0.43	$p < 0.0001$
Site	Buccal mucosa vs Other	1.7	0.90 - 3.0	$p = 0.10$
Treatment	RT/CRT vs OPE	4.4	2.3 - 8.1	$p < 0.0001$

CI, Confidence interval.

Table 3. Multivariate analysis of disease-specific survival rates (Cox proportional-hazards model).

Factors	Category	Hazard ratio	95% CI	*p* value
T	1 or 2 or 3 vs 4	1.3	0.52 - 3.3	$p = 0.57$
N	0 or 1 vs 2	0.81	0.38 - 1.7	$p = 0.60$
Stage	I or II or III vs IV	0.17	0.045 - 0.60	$p = 0.0061$
Treatment	RT/CRT vs OPE	5.3	2.7 - 11	$p < 0.0001$

Multivariate analysis

A multivariate analysis was also conducted for these 4 parameters (T classifications, N classifications, stage and treatment method), and the results are shown in Table 3. Stages I, II and III had a hazard ratio of 0.17 (95% CI 0.045-0.60, $p = 0.0061$) compared to stage IV, and for the treatment method, RT/CRT had a hazard ratio of 5.3 (95% CI 2.7-11, $p < 0.0001$) compared to OPE, which were statistically significant differences. These results were similar to the overall survival rate (data not shown).

Analysis of RT/CRT patients with stage IV

Next, we examined the treatment outcomes of the stage IV and stage IVa patients (excluding inoperable patients). The 5-year disease-specific survival rates of the OPE group were 52% ($n = 48$) and 52% ($n = 46$), for stage IV and IVa, respectively, while those of the RT/CRT group were 0% ($n = 15$) and 0% ($n = 10$), respectively. The RT/CRT group also had significantly poor prognoses compared to the OPE group comparing the stage IV and IVa patients ($p < 0.0001$, $p = 0.00015$, respectively) (Fig. 2B, C). In the patients with stage IVb and IVc, 5 patients who were treated by RT/CRT died within 12 months. On the other hand, 2 patients were treated by OPE. One patient treated by surgery followed by chemotherapy was alive for 47 months after the treatment with disease and the other patient

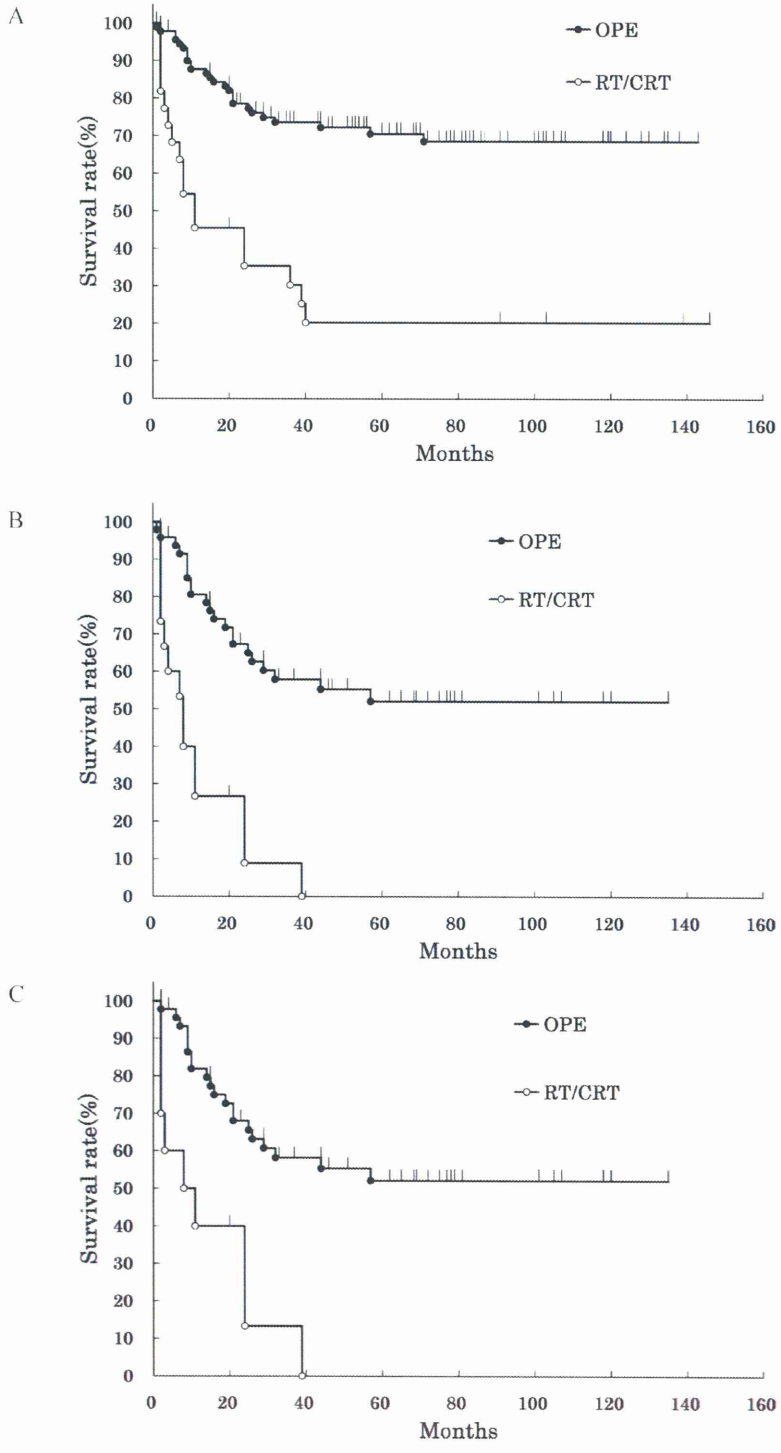

Fig. 2. Disease-specific survival rates by treatment methods.
(A): All patients, (B): Stage IV and (C): Stage IVa
The 5-year disease-specific survival rate of the OPE group showed a significantly good prognosis compared with the RT/CRT group ($p < 0.0001$). Similarly, significant differences were demonstrated in stage IV and IVa patients ($p < 0.0001$, $p = 0.00015$).

Table 4. Disease-specific survival rates for RT/CRT patients

Factors	Category	No. of Patients	5-year survival (%)	p value
Stage	<1> I or II	5	60	1 vs 3 $p = 0.0053$
	<2> III	2	50	
	<3> IV	15	0	
Site	<1> Buccal mucosa	13	18	1 vs 4 $p = 0.76$
	<2> Oral floor	3	33	
	<3> Lower gingiva	2	0	
	<4> Upper gingiva Hard palate	4	25	
Radiation dose	<1> < 60 Gy	5	0	1 vs 2 $p = 0.029$
	<2> = 60 Gy	5	40	
	<3> 60 Gy <	12	21	
Chemo therapy	<1> With	13	19	$p = 0.70$
	<2> Without	9	22	

treated by surgery alone died 1 month after surgery.

Prognostic factors of the RT/CRT patients

The results of analysis of survival rates by factor of the RT/CRT patients are shown in Table 4. In the classification by stage and by radiation dose, a stage IV (0%) and a radiation dose of less than 60 Gy (0%) had significantly poor prognoses, and there were no significant differences related to the site or the presence or absence of chemotherapy. Five patients received a radiation dose of less than 60 Gy, due to the cessation of treatment because of mucositis or other systematic complications in 4 patients and because of a CRT protocol prior to 1999 in 1 patient. Five other patients received a radiation dose of 60 Gy, according to the radiation therapy protocol against early stage cancers or the CRT protocol against advanced stage cancers prior to 1999.

Among the RT/CRT patients with stage IV disease, 11 patients received CRT, while 4 patients received RT only without chemotherapy (RT only). The chemotherapy regimen consisted of iaCDDP in 4 patients, CF in 4 patients, ivCDDP in 1 patient, DCF in 1 patient, and systematic infusion of only fluorouracil in 1 patient due to renal dysfunction. The radiation doses received by CRT patients were over 60 Gy in 8 patients, and 60 Gy or less in 3 patients. Regarding the clinical efficacy of CRT, 6 of the 11 patients treated by CRT demonstrated a complete response of the local tumor in the irradiated volume at the end of the primary treatment, although recurrent tumors were observed in 4 of these 6 patients at the primary site. A regional recurrent tumor was observed in 1 patient and another patient died of colon cancer 20 months after the initial treatment. No specific correlations between clinical efficacy and CRT protocol were found. On the other hand, all 4 patients treated by RT only demonstrated a partial response or no change. Five patients treated by CRT (3 patients) or RT only (2 patients) died (of pneumonia in 4 patients and of a hemorrhagic gastric ulcer in 1 patient) during the initial treatment.

Regarding the clinical efficacy of RT/CRT in patients with stage I, II or III, the local tumors of all 5 patients with stage I or II tumors demonstrated a complete response. Four patients received RT, while the other patient received CRT. Furthermore, 2 of the 4 patients treated by RT only received irradiation therapy consisting of 60 Gy. Primary recurrent tumors were observed in 2 patients treated by RT only who had received radiation doses of 60 Gy and 64.4 Gy. In stage III, one patient treated by CRT had a complete response, while the others treated by RT only demonstrated a partial response.

Analyses of each site

Regarding the various sites, the 5-year disease-specific survival rates according to the stage and treatment method are shown in Table 5. The same tendencies that stage IV and the non-surgical treatment were significant factors for poor prognoses were observed. The reason why the 5-year disease-specific survival rate of buccal mucosa was the worst probably reflects the fact that a large population of RT/CRT treatment patients were included in buccal mucosa compared to other sites.

Discussion

In this study, we investigated the clinical findings of 114 patients with oral SCC excluding tongue SCC, and our analyses led to the conclusion that poor prognostic factors include stage IV disease and the non-surgical treatment. Although the results of the outcomes in this study support the findings of previous reports (Shaha et al. 1984; Hicks et al. 1997; Sessions et al. 2000), we emphasize that the patient outcome for surgery in our patients was almost equal to, or better than those of previous reports (Hicks et al. 1997; Sessions et al. 2000; Diaz et al. 2003) and this study contained some intensive CRT patients, such as iaCDDP (Doweck et al. 2008), CF (Giralt et al. 2000), and

Table 5. Five-year disease-specific survival rates according to stage and treatment strategy in each site.

Buccal mucosa

Factors	Category	No. of Patients	5-year survival (%)	p value
Stage	<1> I	1	100	2 vs 5 $p = 0.00022$
	<2> II	11	61.4	2 vs 6 $p = 0.0014$
	<3> III	6	83.3	3 vs 5 $p = 0.033$
	<4> IVa	16	31.3	3 vs 6 $p = 0.019$
	<5> IVb	2	0	4 vs 5 $p = 0.0044$
	<6> IVc	1	0	4 vs 6 $p = 0.011$
Treatment	<1> Ope	24	64.5	1 vs 2 $p = 0.0057$
	<2> RT/CRT	13	18	

Oral floor

Factors	Category	No. of Patients	5-year survival (%)	p value
Stage	<1> I	6	100	1 vs 4 $p = 0.027$
	<2> II	8	100	1 vs 6 $p = 0.014$
	<3> III	5	83.3	2 vs 4 $p = 0.019$
	<4> IVa	14	34.4	2 vs 6 $p = 0.0082$
	<5> IVb	0		3 vs 6 $p = 0.019$
	<6> IVc	1	0	4 vs 6 $p = 0.022$
Treatment	<1> Ope	32	71.3	1 vs 2 $p = 0.021$
	<2> RT/CRT	3	33.3	

Lower gingiva

Factors	Category	No. of Patients	5-year survival (%)	p value
Stage	<1> I	1	100	4 vs 6 $p = 0.021$
	<2> II	6	75	
	<3> III	0	83.3	
	<4> IVa	20	56.6	
	<5> IVb	0		
	<6> IVc	1	*	
Treatment	<1> Ope	26	75.9	1 vs 2 $p = 0.022$
	<2> RT/CRT	2	0	

Upper gingiva & Hard palate

Factors	Category	No. of Patients	5-year survival (%)	p value
Stage	<1> I	1	100	4 vs 6 $p = 0.021$
	<2> II	2	100	
	<3> III	3	66.7	
	<4> IVa	6	50	
	<5> IVb	1	0	
	<6> IVc	1	0	
Treatment	<1> Ope	10	70	1 vs 2 $p = 0.14$
	<2> RT/CRT	4	25	

*Alive with disease for 47 months.

DCF (Tsukuda et al. 2010).

Regarding the RT/CRT treatment outcomes in this study, the stage IV patients who underwent RT/CRT had poor outcomes. Although a total of 11 stage IV patients received concomitant CRT, only 2 patients showed tumor-free local control after undergoing concomitant CRT. Moreover, one of these 2 patients showed regional recurrence, and only one stage IV patient could demonstrate loco-regional control after CRT. Although some previous reports have described the effectiveness of RT/CRT for advanced head and neck SCC (Doweck et al. 2008; Stenson et al. 2010), non-surgical treatment for advanced oral SCC has reported not to improve prognosis in Japanese Patients (Inagi et al. 2002; Umeda et al. 2004). These results therefore allow us to consider that advanced oral SCC, excluding tongue SCC, might have a worse response to CRT than other head and neck SCC, and careful examination for any local recurrence should be regularly performed even if a complete remission was obtained, because of their high rates of local recurrence after CRT.

Another problem related to RT/CRT indicated in this study was the occurrence of severe complications, such as pneumonia or hemorrhagic gastric ulcers, resulted in poorer prognoses as well as more aggressive features of the tumors. The reasons for such severe complications are as follows. In this study, 4 patients with an advanced age over 80 years were included in the RT/CRT group, and therefore the adaptive rigidification of the RT/CRT protocol and extreme care when performing RT/CRT appear to be necessary to avoid complications and to reduce the number of deaths due to RT/CRT. Second, this study revealed pneumonia to be the most common complication that could cause a worsening of the outcome for elderly patients. Although dysphagia during or after CRT is a well-known issue (Nguyen et al. 2004), appropriate supportive care, such as dental brushing, might be needed for CRT patients as well as for surgical patients (Akutsu et al. 2010).

Since our results of surgical treatment were considered to be acceptable, these results are thought to be adequate baseline data of future clinical studies. These surgical results were obtained based on wide resection of primary tumors, i.e. a 1.5 cm tumor free margin or negative stump in frozen sections. However, as reported recently (Ota et al. 2009), surgical strategies, such as the resection field and neck dissention, should be investigated in future studies.

Post-operative treatment, such as PORT or adjuvant chemotherapy, did not contribute to any improvement in the survival of our patients, and it only represented a relatively

small number of patients. Considering the results of CRT and adjunctive therapy, these results indicate that sensitivity to radiation and to anticancer drugs might be low in oral cancers, excluding tongue cancer, among Japanese patients. The performance of POCRT for the high-risk group has been recommended (Cooper et al. 2004; Bernier et al. 2004) and PORT alone for the moderate risk group according to NCCN Clinical Practice Guidelines for head and neck cancers, but the utility of post-operative treatment in oral cancer remains controversial (Sadeghi et al. 1986; Inagi et al. 2002; Brown et al. 2007). Our results also indicate that a curative operation with a wide resection of the primary tumor may play an important role in achieving prognostic improvements.

In the past, although some studies have reported that the control rate of localized early cancer with radiation is high (Nair et al. 1988; Bachaud et al. 1994; Yorozu et al. 2001), others have reported that the outcomes of surgical treatment surpass those of RT (Cady and Catlin 1969). At the moment, RT is indicated for small primary cancers for the purpose of local control, and it is believed that surgical treatment is the standard for progressive cancer. In addition, based on this analysis, a radiation dose of 60 Gy or more seems to be required for RT/CRT.

Moreover, although there was no survival benefit of RT/CRT for unresectable patients in this limited study, only 1 patient with stage IVc cancer underwent surgery followed by chemotherapy and remained alive with the disease for 47 months. Although anticancer immuno-chemotherapy using cetuximab (Vermorken et al. 2008) and CRT combined with simultaneous CDDP (Adelstein et al. 2003) are now recognized as standard treatments for metastatic or unresectable head and neck SCC, further studies are needed to develop effective strategies for inoperable patients with oral SCC including surgery and tumor dormant chemotherapy.

Conclusions

Our results suggest that a prolonged survival might be expected if surgical treatment is tolerable for patients with advanced oral cancer. In addition, adjunct treatment did not contribute to any improvement in survival in our study. Since this is a limited retrospective study, a prospective study is therefore considered necessary to prove our hypothesis in the future.

Acknowledgments

This study was supported by a Health and Labour Sciences Research Grant for Clinical Cancer Research (H21-tokubetsushitei-hann-2) from the Ministry of Health, Labour and Welfare, Tokyo, Japan.

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Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2012;157:194–201
DOI: 10.1159/000327545

Received: September 18, 2010
Accepted after revision: March 2, 2011
Published online: October 7, 2011

Induction of Thymic Stromal Lymphopoietin Production by Xylene and Exacerbation of Picryl Chloride-Induced Allergic Inflammation in Mice

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Key Words
Allergic inflammation · Thymic stromal lymphopoietin · Xylene

Abstract
Background: Some chemical compounds in the environment worsen allergic inflammation. In this study, we examined whether organic solvents induce the production of thymic stromal lymphopoietin (TSLP) which elicits Th2-type immune responses. ***Methods:*** Organic solvents were painted on the earlobes of BALB/c mice. The expression of TSLP in the ear was determined by ELISA. ***Results:*** Xylene and toluene, but not chloroform or ethyl acetate, induced the expression of mRNA for TSLP in the earlobe tissue. Among the aromatic compounds, xylene, especially *m*-xylene, and trimethylbenzene caused apparent TSLP production. The level of TSLP in the xylene-treated earlobes reached a maximum at 24 h, and TSLP was expressed in epithelial tissues. Production of TSLP was unaffected in mast cell-deficient W/W^v mice but apparently diminished in TNF-α knockout mice and IL-4 receptor knockout mice. Repeated painting of xylene for 7 days induced an increase in the weight of cervical lymph nodes and expression of OX40 ligand, both of which were inhibited in TSLP receptor knockout mice. Xylene promoted the picryl chloride-induced thickening of the ear and IL-4 production, which were reversed in TSLP receptor knockout mice. ***Conclusion:*** Xylene induced TSLP production, resulting in an exacerbation of allergic inflammation. Thus, xylene might be a good tool for examining the roles of TSLP in eliciting allergy in experimental animals.

Introduction

Recently, the number of patients with allergic diseases has been increasing. Exposure to several chemical compounds in the environment might worsen allergies. However, it remains unclear which chemicals modify immune responses and how.

Thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine produced by epithelial cells [1] and mast cells [2], plays an important role in the initiation of allergic inflammation [3]. TSLP production is increased at inflamed sites in patients with severe asthma [4], atopic dermatitis [5] and allergic rhinitis [6]. The allergic inflammation in an animal model of asthma was significantly

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