Glottic cancer in patients without complaints of hoarseness

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ABSTRACT (#55911)

Background: Few studies have investigated the clinical characteristics of patients with glottic cancer (GC) without hoarseness.

Methods: This retrospective clinical study investigated 371 patients with GC.

Results: Thirty-two (8.6%) of the 371 GC patients first presented to hospitals with complaints other than hoarseness. Although proportions of stage I and T1 disease were significantly higher among patients without hoarseness than among those with hoarseness (p=0.0036 and p=0.0004, respectively), survival curves showed no significant differences between groups (p=0.1334).

Conclusions: GC patients without complaints of hoarseness were diagnosed at an earlier stage than those with hoarseness. Accumulation of more cases may lead to better survival of patients with GC without hoarseness compared to those with hoarseness. Checking the larynx of patients without hoarseness or encouraging internists to check the larynx when performing gastroscopic or respiratory examinations may lead to improvement of GC prognosis.

INTRODUCTION

Hoarseness is the most common presenting symptom and the main reason for patients with glottic cancer (GC) to visit the hospital[1,2], and most cases are diagnosed in the early stage[1-3]. Patients with advanced GC may attribute this symptom to a common cold or infection, and the voice remains normal in 10% of cases with T1 or T2 GC[4]. Detection of the tumor at an early or asymptomatic stage is important to improve the survival rate for patients with GC[2]. However, few reports have detailed the relationship between symptoms of hoarseness and prognosis of GC. The objectives of the present study were to delineate the frequency and characteristics of GC cases without symptoms of hoarseness, and to compare prognoses between GC cases with and without complaints of hoarseness.

MATERIALS AND METHODS

Patients

The study population comprised 371 patients (349 men, 22 women) with GC who were first treated at Himeji Red Cross Hospital and its affiliated hospitals between 1994 and 2012. All patients were Japanese and provided written informed consent to participate. All study protocols were approved by the institutional review boards at Himeji Red Cross Hospital and Okayama University Hospital.

For the diagnosis of GC, electroendoscopic observation and histopathological examination were conducted on all patients. When neck metastasis was suspected from the results of physical examination or imaging, fine-needle aspiration cytological testing of neck lymph nodes was carried out. All patients underwent computed tomography (CT), and patients seen after April 2007 also underwent ^{18}F-deoxyglucose positron emission tomography to precisely determine the disease stage.

Treatment and follow-up

Disease was staged according to the 2009 Union for International Cancer Control (UICC) TNM classification. The choice of treatment was at the discretion of the attending physician. Treatments for GC patients consisted of the combination of surgery,

radiotherapy (RT), chemotherapy, and chemoradiotherapy (CRT), as follows: stage I, RT in 180, laser surgery in 20, CRT in 7, radical surgery in 2, no therapy (treatments declined by patient) in 2; stage II, RT in 51, CRT in 36, radical surgery in 6, laser surgery in 2; stage III, RT in 10, CRT in 7, radical surgery in 8, radical surgery + RT in 3, and radical surgery + chemotherapy in 3; and stage IV, radical surgery in 9, radical surgery + chemotherapy in 6, radical surgery + RT in 5, CRT in 4, RT in 3, radical surgery + CRT in 2, and best supportive care in 5. Laser surgery involved partial laryngectomy using a laser under a laryngomicroscope, while radical surgery involved total or partial laryngectomy through a skin incision. Chemotherapeutic regimens mainly consisted of cisplatin and 5-fluorouracil, and sometimes included docetaxel. TS1 was sometimes used as a substitute for these agents according to the stage of the disease, performance status, and patient age. When the tumor did not show complete response or recurred after the first treatment, additional treatments were administered. Patients were followed until death or the last medical examination.

Statistical analysis

The significance of differences in baseline characteristics was determined using the chi-square test or unpaired *t*-test, as appropriate. Survival times were defined as the

interval from the detection of GC to death or last follow-up examination. Survival was estimated using the Kaplan-Meier method, and differences in survival between groups were assessed with the log-rank test. Patients were treated as censored when lost to follow-up. Because the number of patients with stage III or IV disease was relatively smaller compared to those with stage I or II, we analyzed the data for stage III and IV disease together. We evaluated the association between the existence of hoarseness and patients profiles (stage, sex, proportion of smokers, and disease-specific survival rate). In the present study, “hoarseness” did not mean clinical findings based on voice evaluation criteria like the GRABS scale (grade, roughness, breathiness, asthenia, and strain scale), but patients’ complaints for subjective voice abnormalities. All analyses were performed using SPSS version 21.0J software (SPSS, Armonk, NY, USA). Values of $p < 0.05$ were accepted as significant, while values of $p < 0.1$ were considered to indicate a tendency.

RESULTS

Patient characteristics and overall outcomes

The study population included 349 men and 22 women, with a mean age at the time of GC detection of 68.0 years (range, 33-95 years). Mean duration of follow-up after detection of GC was 64.1 months (range, 1-208 months). Smoking status was confirmed in 351 patients, of whom 287 (81.8%) were ever-smokers. Of the 371 patients with GC, 211 (56.9%) showed stage I disease, 95 (25.6%) had stage II, 31 (8.4%) had stage III, and 34 (9.2%) had stage IV (Table 1). The 5-year disease-specific survival rates of patients with stages I, II, and III-IV were 98.1%, 94.5%, and 67.5%, respectively, while the 10-year disease-specific survival rates were 98.1%, 87.5%, and 67.5%, respectively (Fig. 1). Significant differences in disease-specific survival rate were evident between stages I and II (p=0.0099), and between stages II and III-IV (p=0.0003).

Patients without complaints of hoarseness

At the time of GC detection, 32 (8.6%) of the 371 GC patients did not show any complaints of subjective voice changes (**Table 2**). Among these, 25 cases (78%) were identified by the department of otolaryngology, and the chief complaints in these

cases were: sore throat or foreign body sensation in the neck, 10 (31.3%); nasal symptoms, 6 (18.8%); upper respiratory inflammation, 4 (12.5%); and others, 5 (15.6%) (**Table 3**). In the remaining 7 cases (21.9%), GC was found during gastroscopic or bronchoscopic examinations. Smoking status was confirmed in 31 of these 32 patients, of whom 29 (93.5%) were smokers. These 32 patients did not include any professionals with significant occupational voice use like singers or call center operators.

Comparison between cases with and without complaints of hoarseness

UICC staging of the 339 patients with complaints of hoarseness was stage I in 185 (56.2%), stage II in 85 (25.8%), stage III in 28 (8.5%), and stage IV in 31 (9.4%). Among the patients without hoarseness, GC was stage I in 26 (81.3%), stage II in 4 (12.5%), stage III in 1 (3.1%) and stage IV in 1 (3.1%). Proportions of patients with stage I and T1 disease were significantly higher among patients without hoarseness than among patients with hoarseness (stage I, $p=0.0036$; T1, $p=0.0004$). No significant differences in the proportion of males to females was evident between patients with and without hoarseness ($p=0.76$). Although there was also no significant difference in the proportion of smokers between groups with and without hoarseness, the proportion of smokers tended to be higher among patients without hoarseness than among patients

with hoarseness (p=0.075) (**Tables 4, 5**). All patients with GC without hoarseness remained alive during the observation period. However, disease-specific survival rates showed no significant difference between GC patients with and without hoarseness (p=0.133) (**Fig. 2**).

DISCUSSION

In the 1960s, before laryngeal fiberscopy became available, only 10-18% of GC patients were identified in stage I or II[5, 6]. Since the development of the laryngeal fiberscope, the proportion of stage I-II among all GC patients has improved to 74.1-92.3%[1-3], and the proportion in the present study was 82.5%. Early detection of GC has clearly improved considerably, but now seems to have reached a plateau[1].

Patients with GC show a better prognosis than patients with supraglottic cancer, due at least in part to a more favorable stage distribution at the time of diagnosis, because GC becomes symptomatic sooner than supraglottic cancer[7]. In over 95% of GC patients, the first symptom was hoarseness or vocal change[1, 2]. In the present study, 339 (91.4%) of the 371 patients complained of hoarseness at first presentation. The only way to improve the survival rate for GC may be to detect tumors at an earlier or asymptomatic stage[2]. Psychoacoustic evaluation identifies a normal voice in 10% of cases with T1 and T2 GC[4], and the majority of GC cases without the symptom of hoarseness were actually early stage in the present study. In particular, all 7 cases of GC without complaints of hoarseness detected by internists performing gastroscopic or bronchoscopic examination were diagnosed at stage I. Tobacco and alcohol represent well-known risk factors for the development of malignancies in the head and neck

region and upper gastrointestinal tract[8]. The Japan Tobacco Company reported smoking prevalence of 32.2% for men and 10.5% for women in Japan[9], and 81.8% of GC patients in the present study were smokers. In our study, the percentage of smokers was higher among GC patients without complaints of hoarseness than GC patients with hoarseness. Although we did not study the past medical history of patients in the present study, previous gastric surgery has also been associated with an increased risk of laryngeal cancer, and acid pepsin-related diseases in the upper digestive tract (esophagitis, gastritis, duodenitis, or gastric ulcer) were more frequent in patients with laryngeal cancer than in those without[10]. General practitioners and internists should thus be encouraged to give special attention to the larynx of patients at risk of developing laryngeal cancer[2], which may lead to improvements in the prognosis of GC.

It was a limitation of our study that “without hoarseness” in the present study did not always mean normal voice quality. There are considerable differences among patients in the degree to which patients themselves are inconvenienced in regard to their voices because of the differences in vocal demands depending on individual factors such as sex or profession[11]. Although the GC patients without symptoms of hoarseness included many smokers in the present study, smokers may be more tolerant to hoarse

voice than non-smokers. Since people from different cultures may perceive voice problem differently[12], the results of this study may differ if performed in other countries.

Eleven GC patients (3%) in the present study were found among the population who visited hospitals because of nasal or other symptoms without any pharyngeal or laryngeal symptoms. Although performing laryngeal fiberscopic examination on all outpatients seen in otolaryngology departments is clearly not feasible, care must be taken to avoid overlooking suspicious signs of laryngeal cancer despite an absence of voice symptoms, particularly among patients with high-risk factors.

CONCLUSIONS

GC patients without complaints of hoarseness were diagnosed at earlier stages than patients with hoarseness. Accumulation of more cases may lead to better survival of patients with GC without hoarseness compared to patients with hoarseness. It is important not to overlook signs of GC among patients without complaints of hoarseness. In addition, encouraging internists to check the larynx during gastroscopic or bronchoscopic examinations may lead to improvements in GC prognosis.

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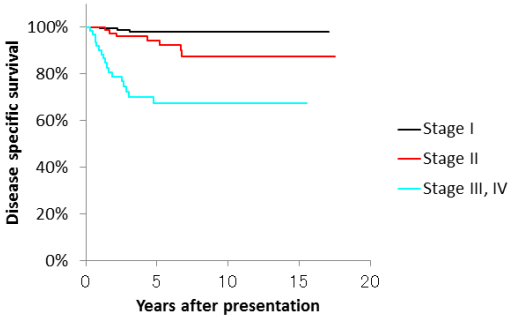
Figure legends

Figure 1. Disease-specific survival rate of GC patients with stages I, II, or III-IV

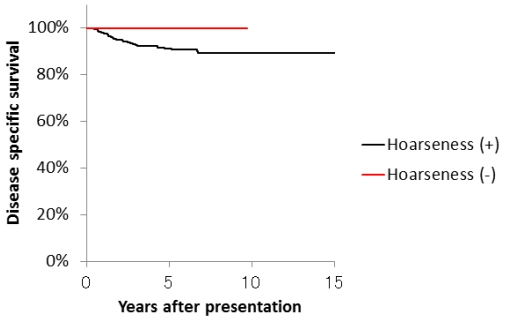
Figure 2. Disease-specific survival rate in patients with and without hoarseness

Figure 1



Stage	Survival rate		*p*
	5-year	10-year	
I	98.1%	98.1%	
			0.0099**
II	94.5%	87.5%	
			0,0003**
III, IV	67.5%	67.5%	

Figure 2



Hoarseness	Survival rate		*p*
	5-year	10-year	
Positive	91.1%	89.1%	0.1334
Negative	100.0%		

Table 1. TNM staging of all patients with GC

Stage	T1	T2	T3	T4	Total
N0	213 (2)	96 (1)	28 (2)	10	347
N1	1	2	2	2	7
N2		3	6 (1)	6	15
N3		1		1	2
Total	214	102	36	19	371

Stage	n (%)
I	211 (56.9%)
II	95 (25.6%)
III	31 (8.4%)
IV	34 (9.2%)
Total	371

Numbers in parentheses indicate numbers of patients with distant metastasis.

GC: glottic cancer.

Table 2. Complaints of GC patients without hoarseness

Symptoms	n	%
Pharyngeal symptoms	10	31.3%
sore throat	6	
foreign body sensation in the larynx	4	
Gastroscopic or bronchoscopic examination	7	21.9%
gastroscope	5	
bronchoscope	2	
Nasal symptoms	6	18.8%
nasal bleeding	4	
parasinusitis	2	
Cough and/or sputum	4	12.5%
Others	5	15.6%
Total	32	

GC: glottic cancer.

Table 3. Characteristics of 5 GC patients with other symptoms

Case	Age	Sex	TNM	Symptom	Diagnosis for chief complaint	Opportunity for diagnosis of GC
1	87	M	T1bN0M0	bilateral ear fullness	patulous Eustachian tube	investigation for nasopharynx
2	59	M	T1aN0M0	left-sided ear fullness	left otitis media with effusion	investigation for nasopharynx
3	55	M	T1aN0M0	dizziness	(-)	screening for larynx
4	69	M	T2N0M0	presyncope	(-)	computed tomography
5	70	M	T1aN0M0	neck swelling	parotid benign tumor	screening for larynx

(-) Cause of chief complaint was unclear.

GC: glottic cancer.

Table 4. TNM staging of patients with and without hoarseness

A) TNM staging of patients with hoarseness

Stage	T1	T2	T3	T4	Total
N0	186 (1)	92 (1)	28 (2)	10	316
N1	(-)	2	2	2	6
N2	(-)	3	6 (1)	6	15
N3	(-)	1	(-)	1	2
Total	186	98	36	19	339

B) TNM staging of patients without hoarseness

Stage	T1	T2	T3	T4	Total
N0	27 (1)	4	(-)	(-)	31
N1	1	(-)	(-)	(-)	1
N2	(-)	(-)	(-)	(-)	(-)
N3	(-)	(-)	(-)	(-)	(-)
Total	28	4	(-)	(-)	32

(-) No patients fell into these conditions.

Table 5. TNM stage for 371 cases with GC

Characteristics	Hoarseness		*p*
	Positive	Negative	
Stage I	185/339 (54.6%)	26/32 (81.3%)	0.0036**
T1	186/339 (54.9%)	28/32 (87.5%)	0.0004**
Stage I-II	276/339 (81.4%)	30/32 (93.8%)	0.0793
N0	316/339 (93.2%)	31/32 (96.9%)	0.6682
Smoking habit	258/320 (80.6%)	29/31 (93.5%)	0.0752

** Significant difference between groups.

GC: glottic cancer.