Available online at www.sciencedirect.com
ScienceDirect
Journal of the Chinese Medical Association 74 (2011) 220–225
www.jcma-online.com

Original Article

Management of base of tongue squamous cell carcinoma: Experience with 85 patients in Taipei Veterans General Hospital

Wei-Chi Tseng [a,b], Shyue-Yih Chang [a,b], Pen-Yuan Chu [a,b], Shyh-Kuan Tai [a,b,c], Yi-Feng Wang [a,b,c], An-Suey Shiao [a,b], Tung-Lung Tsai [a,b,c,*]

[a] *Division of Laryngology—Head and Neck Surgery, Department of Otolaryngology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[c] *Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*

Received August 24, 2010; accepted December 20, 2010

Abstract

Background: The optimal treatment of base of tongue squamous cell carcinoma (BOTSCC) remains controversial. To optimize treatment planning, this study analyzed the outcomes of patients with BOTSCC treated in Taipei Veterans General Hospital.
Methods: Retrospective chart reviews were performed for 107 patients with BOTSCC from January 1990 to December 2004, and 85 patients were included, with a mean follow-up interval of 38 months. Patients were divided into surgical and radiotherapy/chemoradiation therapy (RT/CRT) groups. Potentially significant variables for survival were analyzed.
Results: The 3-year overall survival (OS) and disease-free survival rates were 40% and 37.1%, respectively. No significant differences in the patient and disease characteristics between the surgical ($n = 39$) and RT/CRT groups ($n = 46$) were found. Advanced overall stage ($p = 0.034$), cervical lymph node metastasis ($p = 0.007$), and regional recurrence ($p = 0.024$) were poor prognostic factors for OS. In early-stage disease (Stages I and II), the 3-year OS was higher in the surgical group (68.6%) than in the RT/CRT group (37.5%), but the significance was only borderline ($p = 0.071$). There was no significant difference in the 3-year OS between the patients in the surgical and CT/CRT groups with advanced-stage disease. In the surgical group, lymphovascular permeation ($p = 0.015$) and soft-tissue involvement ($p = 0.01$), determined by pathologic examination, were poor prognostic factors for OS. Recurrence occurred in 35 patients (41.2%), with no significant difference in local, regional, or distant control between the surgical and RT/CRT groups.
Conclusion: These findings emphasize the importance of neck disease control in the treatment of BOTSCC. Although currently, RT/CRT is used more frequently, surgery may still have a role in the treatment of early-stage disease. Both surgery with adjuvant therapy and RT/CRT produced equivalent survival rates in the treatment of advanced-stage disease, but the recurrence rate was unsatisfactory. A more effective treatment modality with less early and late toxicity is needed.

Keywords: Base of tongue; Chemoradiation; Oropharynx; Radiation; Squamous cell carcinoma

1. Introduction

Although research has reported good results of oropharyngeal squamous cell carcinoma treated by chemoradiation therapy (CRT),[1,2] the optimal treatment of base of tongue squamous cell carcinoma (BOTSCC) remains controversial.[2,3] In BOTSCC, reports indicate that the treatment response is significantly worse than that for other oropharyngeal subsites.[2] Furthermore, evidence from a population-based study of the United States National Cancer Data Base, which included 16,188 cases of BOTSCC, did not support the superiority of nonsurgical treatment because it failed to provide favorable survival outcome.[3] Patients with favorable T1 and T2 lesions can be treated with surgery or radiotherapy (RT) alone. Radical

* Corresponding author. Dr. Tung-Lung Tsai, Department of Otorhinolaryngology—Head and Neck Surgery, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: tltsai@vghtpe.gov.tw (T.-L. Tsai).

1726-4901/$ - see front matter
doi:10.1016/j.jcma.2011.03.007

tumor resection followed by RT has been the standard therapy in patients with advanced BOTSCC because of higher rates of locoregional control, but this often results in dysfunction of swallowing and speech.[4] Nonsurgical treatments with CRT have shown equivalent oncologic results. However, debates about whether surgery with or without adjuvant therapy produces better oncologic results than nonsurgical protocols, particularly for advanced tumors, are ongoing.

Poor control of disease in patients with BOTSCC has been attributed to the advanced stage of disease when diagnosed, which results from many factors including tumor behavior, anatomic factors, and the patient's personality and socioeconomic status. The purpose of this study was to analyze the clinical presentation, treatment response, failure patterns, and rates of survival among patients with BOTSCC treated in Taipei Veterans General Hospital (VGHTPE) to optimize the planning and choice of treatment modality.

2. Methods

This study was approved by the Institutional Review Board of VGHTPE. From January 1990 to December 2004, 107 patients with BOTSCC were seen at the Department of Otorhinolaryngology—Head and Neck Surgery of VGHTPE. Their medical records were reviewed retrospectively. All the diagnoses were proved by biopsy and pathologic examination. The tumors were re-staged retrospectively based on the 2002 criteria of the American Joint Committee on Cancer classification.[5] Patients who received any type of curative resection at the primary site with or without neck dissection (ND) as initial treatment were defined as the surgical group. The RT/CRT group was composed of patients who were treated with RT or CRT as definitive therapy. Patients who underwent salvage surgery performed after the completion of CRT or RT were not included in the surgical group. The exclusion criteria for analysis were the presence of other underlying malignancies, previous treatment of BOTSCC, and distant metastasis (DM) at the time of diagnosis. Of the 107 patients identified, 4 patients had metastatic disease at the time of diagnosis and 18 patients did not receive curative treatment at VGHTPE. Thus, 85 patients were included in this study.

2.1. Statistical analysis

Overall survival (OS) was defined as the interval between the initial date of treatment and the date of death. The interval between the initial date of treatment and the date of the last consultation was defined as censored times. For the

Table 1
Patients' characteristics

Characteristics	All patients ($n = 85$)	Surgery ($n = 39$)	Nonsurgery ($n = 46$)
Mean follow-up (mo)	38.0 (1.3–180.5)	46.8 (2.37–180.5)	29.5 (1.3–153.3)
Sex			
Men	77 (90.6)	34 (87.2)	43 (93.5)
Women	8 (9.4)	5 (12.5)	3 (6.5)
Age (yr)	57 (28–84)	57.6 ± 11.7 (30–83)	56.5 ± 13.2 (28–84)
Clinical stage			
Early (I, II)	18	10 (25.6)	8 (17.4)
Late (III, IV)	67	29 (74.4)	38 (82.6)
T stage			
T1	10 (11.8)	8 (20.5)	2 (4.3)
T2	35 (41.2)	13 (33.3)	22 (47.8)
T3	24 (28.2)	11 (28.2)	13 (28.3)
T4a	11 (12.9)	5 (12.8)	6 (13)
T4b	5 (5.9)	2 (5.1)	3 (6.5)
N stage			
N0	25 (29.4)	12 (30.8)	13 (28.3)
N1	13 (15.3)	5 (12.8)	8 (17.4)
N2a	4 (4.7)	2 (5.1)	2 (4.3)
N2b	22 (25.9)	10 (25.6)	12 (26.1)
N2c	13 (15.3)	7 (17.9)	6 (13)
N3	8 (9.4)	3 (7.7)	5 (10.9)
Overall stage			
I	5 (5.9)	4 (10.3)	1 (2.2)
II	13 (15.3)	6 (15.4)	6 (15.2)
III	13 (15.3)	5 (12.8)	7 (17.4)
IVA	41 (48.2)	20 (51.3)	21 (45.7)
IVB	13 (15.3)	4 (10.3)	9 (19.6)

Data are presented as number ± standard deviation with percentage or range in parentheses.

determination of disease-free survival (DFS), intercurrent deaths and deaths because of second primary tumors, as well as patients alive without recurrence, were regarded as censored observations. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses. OS and DFS were generated by the Kaplan-Meier method, and statistically significant differences between survival rates were determined by log-rank test. Multivariate analysis was conducted by the Cox regression method. Categorical and continuous data were evaluated by the χ^2 method and *t* test, respectively. Probability values of less than 0.05 were considered statistically significant.

3. Results

3.1. Clinical data

Table 1 shows the details of clinical tumor, nodes, and metastases stages and treatment methods. Of the known risk factors, 72.9% and 60.5% of the patients used tobacco and alcohol, respectively. Fig. 1 includes the initial presenting symptoms. The most common symptoms were tongue pain (31.7%), neck mass (28.2%), and odynophagia (23.5%). The mean symptomatic period before seeking care was 4 months. Midline lesions were present in 14.3% of patients. Table 2 summarizes tumor appearances and the sites of tumor extensions. Only 18 patients (21.2%) had diagnoses of early-stage disease, and 60 patients (70.6%) had cervical lymph node (LN) metastasis when their conditions were diagnosed. The patient and disease characteristics were not significantly different between the surgical ($n = 39$) and RT/CRT groups ($n = 46$), as indicated in Table 1.

In the surgical group, larger surgical defects were reconstructed with pectoralis major myocutaneous flaps in 12 patients and a rotational tongue flap in 1 patient. ND was performed in 32 patients (82.1%), including ipsilateral dissection in 23 (71.9%) and bilateral dissection in 9 patients (23.1%). Seven NDs were elective for patients with clinical N0 disease.

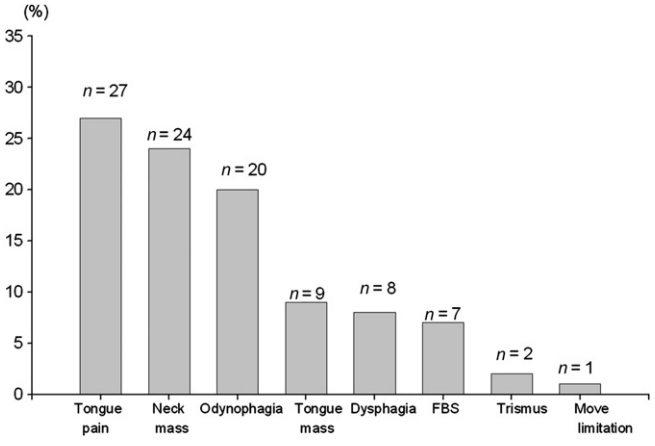

Fig. 1. Distribution of initial presenting symptoms. FBS = foreign body sensation.

Table 2
Appearance of tumors and the sites of tumor extension

	n (%)
Tumor appearance	
Exophytic	45 (52.9)
Endophytic	15 (17.6)
Ulcerative	25 (29.4)
Site of tumor extension	
Vallecula	23 (27.1)
Midline cross	21 (24.7)
Oral tongue	15 (17.6)
Ipsilateral tonsil	13 (15.3)
Ipsilateral pharyngeal wall	12 (14.1)
Floor of mouth	9 (10.6)
Epiglottis	9 (10.6)
Arytenoid-epiglottic fold	7 (8.2)
Pre-epiglottic space	5 (5.9)
Pyriform sinus	4 (4.7)
Skull base	1 (1.2)
Soft palate	1 (1.2)
Gingiva	1 (1.2)
Retromolar trigone	1 (1.2)
Mandible	1 (1.2)
Hyoid bone	1 (1.2)
Neck soft tissue	1 (1.2)

The grades of tumors in the final pathology reports were well differentiated in 6 (15.4%), moderately differentiated in 19 (48.7%), and poorly differentiated in 5 (12.8%). For the 33 tumors with available surgical margin reports, 27 (69.3%) had negative margins and 6 (15.4%) had positive margins. Cervical LN metastasis was confirmed in 26 patients (66.6%), and extracapsular spreading of tumor cells was found in four patients (10.2%). The mean number of neck LN metastases was 4.2 (range, 1–10). Occult neck metastasis was confirmed in 1 of 7 (14.3%) patients with clinical N0 disease after ND. According to the final pathology report, the overall stage was downgraded in three patients (7.7%), from Stage IV to III in one patient and from Stage II to I in two patients; and it was upgraded in two patients (5.1%), from Stage I to II in one patient and from Stage II to III in one patient.

Twenty-nine patients (74.4%) received postoperative RT, and three patients (7.7%) received postoperative CRT. The indications for postoperative adjuvant therapy were T4 tumor determined by pathology, advanced N2 or N3 neck disease, and unfavorable pathologic factors such as perineural invasion, lymphovascular permeation, tumor emboli, extracapsular spreading, and positive surgical margins. All patients who underwent adjuvant therapy received continuous-course external-beam RT to the primary cancer with once-daily fractionation. The mean total dose was 6,180 cGy, with a mean fraction of 31.

In the RT/CRT group, 16 patients (18.8%) received RT alone and 30 patients (35.3%) received primary CRT with the aim of preserving the tongue and its function. The intended dose of irradiation to the primary site and gross lymphadenopathy (≥1 cm) was 7,000 cGy, whereas it was 5,000 cGy to the N0 neck. The mean total dose was 6,910 cGy to the primary site, with a mean fraction of 37 (range, 18–61). The

Table 3
Three-year overall survival rates (calculated by Kaplan-Meier method) according to the T, N, and overall stages

	N0	I	II	III	IV_A	IV_B
T stage (%)		70	34.3	45.8	25	
N stage (%)	56	38.5	35.9	12.5		
Overall stage (%)		83.3	50	46.2	39	7.7

mean overall treatment period was 54.9 days (range, 31–77 days). Since 2000, CRT has been the most frequently used treatment of oropharyngeal cancer at VGHTPE. The percentage of patients treated with RT/CRT increased from 46% in the 1990s to 65% after January 2000, and this increase was significant ($p = 0.01$).

3.2. Oncologic results

With a mean follow-up of 38 months (range, 1.3–180.5 months), 51 of 85 patients died, 20 patients from the surgical group and 31 patients from the RT/CRT groups. The 3-year OS and DFS were 40% and 37.1%, respectively. The 3-year local and regional control rates were 77.1% and 81.8%, respectively. Table 3 summarizes the 3-year survival rates according to the T, N, and overall stages. As shown in Table 4, the prognostic factors that affected OS unfavorably were advanced overall clinical stage ($p = 0.034$), cervical nodal involvement ($p = 0.007$), and regional recurrence ($p = 0.024$). Multivariate analysis found no specific independent prognostic factor.

In the surgical group, pathology results indicating soft-tissue involvement (tumor extension into adjacent fat, muscle, salivary gland, or skin) and lymphovascular permeation were significant poor prognostic factors for 3-year OS (Figs. 2 and 3). Among patients with early-stage (Stages I and II) disease, there was a trend toward a survival benefit with surgery compared with RT/CRT; the OS rates were 68.6% and 37.5%, respectively, with borderline significance ($p = 0.071$).

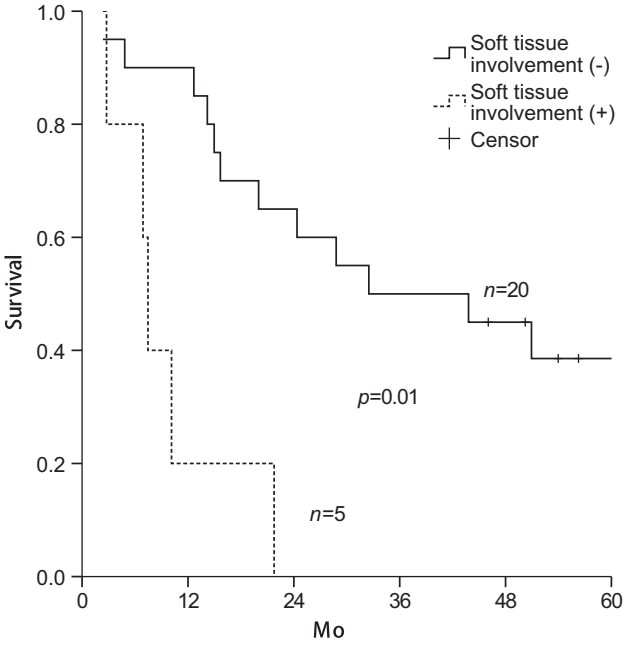

Fig. 2. Kaplan-Meier projected overall survival in the surgical groups with/without soft-tissue involvement. All five patients in the soft-tissue involvement (+) group died; 10 of 20 patients in the soft-tissue involvement (−) group died.

A total of 35 patients suffered from recurrence/DM (Table 5). Six patients (7.1%) had metastasis to the lung, which was the most common site for DM. The mean time to

Table 4
Analysis of the prognostic factors influencing 3-year OS

Characteristics	*n*	Univariate analysis			Multivariate analysis		
		3-yr OS	95% CI	*p*	RR	95% CI	*p*
Sex				NS			
Male	77	41.6	30.6–52.6				
Female	8	25	0–55				
Age				NS			
≦60 yr	47	46.8	32.5–61.1				
>60 yr	38	31.6	16.9–46.3				
Clinical stage				0.034			NS
Early (I, II)	18	61.1	38.5–83.6				
Late (III, IV)	67	34.3	22.9–45.7		1.69	0.5–5.78	
T stage				NS			
T1, 2	45	42.2	27.7–56.7				
T3, 4	40	37.5	22.4–52.6				
N stage				0.007			NS
N(−)	25	56	55.3–117.1				
N(+)	50	33.3	26.5–47.3		1.16	0.41–3.31	
Local recurrence				NS			
Yes	13	18.8	13.6–48.6				
No	72	44.9	39.2–70.5				
Regional recurrence				0.024			NS
Yes	13	8.3	6.2–31.7		1.69	0.85–3.37	
No	72	45.2	41.1–80				

CI = confidence interval; NS = non-significant; OS = overall survival; RR = risk ratio.

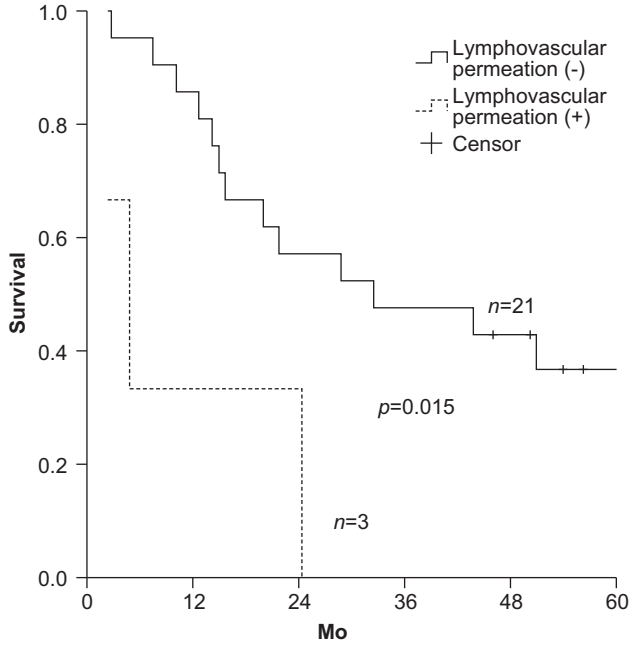

Fig. 3. Kaplan-Meier projected overall survival in the surgical group with/without lymphovascular permeation. All three patients in the lymphovascular permeation (+) group died; 11 of 21 patients in the lymphovascular permeation (−) group died.

tumor recurrence from initial treatment was 10.8 months (range, 3.2−31.3 months), and 91.4% of recurrences occurred within 2 years after initial treatment. Recurrence occurred less frequently in N(−) disease (28%) than in N(+) disease (46.7%). There was no significant difference in local/regional/distant control when the surgical and RT/CRT groups were compared. In the surgical group, only soft-tissue involvement was a significant negative pathologic prognostic factor for the rate of regional control ($p < 0.001$).

Twenty-six patients (74.3%) with recurrence/DM received salvage treatments (Table 6). However, the rate of successful salvage was very poor; and the mean survival after recurrence was 13.3 months (range, 0.2−92 months). There were no significant prognostic factors affecting the rate of survival after salvage among patients with recurrence. Among patients with early-stage disease who had surgical intervention ($n = 10$), a midline location of the primary tumor ($n = 2$) was associated with a higher recurrence rate compared with tumors with laterality ($n = 8$); the recurrence rates were 50% and 12.5%, respectively. A second primary malignancy occurred in eight patients (9.4%), and the oral cavity ($n = 2$) was the most common site.

Table 6
Salvage treatments for recurrence/distant metastasis

Salvage treatment	*n*
Surgery alone	6
Surgery followed by radiation	3
Chemoradiation	2
Radiation alone	4
Chemotherapy alone	11
Total	26

4. Discussion

Because a large portion of the whole tongue is occupied by the BOT, tumors can infiltrate deeply before significant symptoms occur. Clinically, a tumor in this area is difficult to detect in the early stages. Gourin et al.[6] reported that up to 91% of their patients presented with T3/4 disease. In our study, 48.2% presented with T3/4 stage, and 71.6% presented with LN metastasis at the time of diagnosis. In this study, tongue pain was the most common symptom of BOTSCC. The relatively asymptomatic nature of BOTSCC at an early stage and its high cervical LN metastasis rate make late-stage disease common at the time of diagnosis, which results in a poor survival rate.

In the early stage (Stages I and II) of BOTSCC, survival rates of patients treated with RT, surgery, or combined modalities have been reported to be between 50% and 70%.[7] In our patients with early-stage disease, the 3-year OS was 61.1%, and the surgical group had a slightly superior survival rate compared with RT/CRT treatment. This finding is compatible with the result of the United States National Cancer Data Base analysis, which revealed that patients treated by surgery with or without RT have favorable survival in early-stage disease.[3] The possible reason for our finding may be that the survival after salvage for recurrence is relatively higher in the surgical group (50%) as opposed to the nonsurgery group (0%) in early-stage patients. After high-dose radiotherapy as primary treatment in the nonsurgery group, most recurrent oropharyngeal cancer patients were poor candidates for salvage treatment.[8] Higher local recurrence rates occurred in midline lesions as opposed to those with laterality among the surgical group. Difficulty in exposure of midline lesions by traditional surgical approaches may be the

Table 5
Treatment failure patterns ($n = 35$)

Failure pattern	Number of patients	Surgery and adjuvant therapy ($n = 16$)	Chemoradiation therapy ($n = 14$)	Radiotherapy alone ($n = 5$)
Local recurrence	13	6	4	3
Locoregional recurrence	1	1	0	0
Neck recurrence	12	4	6	2
Distant metastasis and local recurrence	2	1	1	0
Distant metastasis and locoregional control	7	4	3	0

reason, and as a result, nonsurgical treatment may be more suitable for such lesions.

The treatment of advanced-stage (Stages III and IV) BOTSCC often requires a multimodal strategy for adequate disease control, such as surgery plus postoperative RT or combined CRT. Some authors have suggested primary RT,[9,10] whereas others promote surgery with adjuvant therapy.[3,11] If surgery was the primary treatment, data support the combination of postoperative RT for patients with advanced disease.[3,12,13] For advanced-staged BOTSCC treated by surgery and postoperative RT, the 5-year survival rate was approximately 60%.[12–14]

In head and neck cancers, locoregional control of advanced-stage disease was improved through the use of more aggressive courses of radiation or the addition of chemotherapy.[15] However, the late toxic effects of CRT are no less severe than the complications of surgery. A high rate of dysphagia, aspiration, and long-term gastric tube dependence was reported among patients with BOTSCC treated by CRT.[16–18] In advanced BOTSCC, organ preservation by nonsurgical treatment does not always promise the preservation of function and improvement in quality of life.

From our study, advanced overall stage, cervical LN metastasis, and regional recurrence were prognostic factors that indicated poor OS in univariate analysis. The 3-year OS rate decreased from 56% to 33.3% if neck metastasis occurred. Unfavorable histopathologic features including positive surgical margin, perineural invasion, lymphovascular permeation, tumor emboli, node level, and number, size, and presence of extracapsular extension have been shown to be associated with increased risk of recurrence in head and neck cancers.[19] In the surgical group, lymphovascular permeation and soft-tissue involvement were significant poor prognostic factors for OS. This study found that neck recurrence was almost twice as likely to occur in histopathologically determined N(+) necks compared with N(−) necks (46.7% *vs.* 28%, respectively), and Leemans et al reported a similar result.[20] These findings highlight the importance of disease control in neck for the treatment of BOTSCC. Postoperative adjuvant CRT was highly recommended to reduce the negative effect of these risk factors in BOTSCC.

In conclusion, BOTSCC is an aggressive disease that is often diagnosed at a late stage and is characterized by poor survival rates despite improvements in current standard therapy. Advanced overall stage, cervical LN metastasis, and regional recurrence were identified as poor prognostic factors in our patients with BOTSCC. The analysis of surgical group suggested that neck control is very important for OS. Although RT/CRT treatment modalities are used more frequently, surgery may still have a role in the treatment of patients with BOTSCC at an early stage because of better salvage survival rate after recurrence. A more effective treatment modality with less early and late toxicity is needed for the treatment of BOTSCC.

References

1. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;**363**:24–35.
2. Sundaram K, Schwartz J, Har-El G, Lucente F. Carcinoma of the oropharynx: factors affecting outcome. *Laryngoscope* 2005;**115**:1536–42.
3. Zhen W, Karnell LH, Hoffman HT, Funk GF, Buatti JM, Menck HR. The National Cancer Data Base report on squamous cell carcinoma of the base of tongue. *Head Neck* 2004;**26**:660–74.
4. Han P, Hu K, Frank DK, Sessions RB, Harrison LB. Management of cancer of the base of tongue. *Otolaryngol Clin North Am* 2005;**38**:75–85.
5. Greene FLPD, Fleming ID, Fritz AG, Blach CM, Haller DG. *American Joint Committee on cancer staging manual*. 6th ed. New York: Lippincott-Raven; 2002.
6. Gourin CG, Johnson JT. Surgical treatment of squamous cell carcinoma of the base of tongue. *Head Neck* 2001;**23**:653–60.
7. Sessions DG, Lenox J, Spector GJ, Chao C, Chaudry OA. Analysis of treatment results for base of tongue cancer. *Laryngoscope* 2003;**113**:1252–61.
8. Röösli C, Studer G, Stoeckli SJ. Salvage treatment for recurrent oropharyngeal squamous cell carcinoma. *Head Neck* 2010;**32**:989–96.
9. Harrison LB, Lee HJ, Pfister DG, Kraus DH, White C, Raben A, et al. Long-term results of primary radiotherapy with/without neck dissection for squamous cell cancer of the base of tongue. *Head Neck* 1998;**20**:668–73.
10. Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Moore-Higgs GJ, Cassisi NJ. Is radiation therapy a preferred alternative to surgery for squamous cell carcinoma of the base of tongue? *J Clin Oncol* 2000;**18**:35–42.
11. Nisi KW, Foote RL, Bonner JA, McCaffrey TV. Adjuvant radiotherapy for squamous cell carcinoma of the tongue base: improved local-regional disease control compared with surgery alone. *Int J Radiat Oncol Biol Phys* 1998;**41**:371–7.
12. Steiner W, Fierek O, Ambrosch P, Hommerich CP, Kron M. Transoral laser microsurgery for squamous cell carcinoma of the base of the tongue. *Arch Otolaryngol Head Neck Surg* 2003;**129**:36–43.
13. Zelefsky MJ, Harrison LB, Fass DE, Armstrong JG, Shah JP, Strong EW. Postoperative radiation therapy for squamous cell carcinomas of the oral cavity and oropharynx: impact of therapy on patients with positive surgical margins. *Int J Radiat Oncol Biol Phys* 1993;**25**:17–21.
14. Rollo J, Rozenbom CV, Thawley S, Korba A, Ogura J, Perez CA, et al. Squamous carcinoma of the base of the tongue: a clinicopathologic study of 81 cases. *Cancer* 1981;**47**:333–42.
15. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. *Lancet* 2000;**355**:949–55.
16. Shiley SG, Hargunani CA, Skoner JM, Holland JM, Wax MK. Swallowing function after chemoradiation for advanced stage oropharyngeal cancer. *Otolaryngol Head Neck Surg* 2006;**134**:455–9.
17. Teguh DN, Levendag PC, Noever I, van Rooij P, Voet P, van der Est H, et al. Treatment techniques and site considerations regarding dysphagia-related quality of life in cancer of the oropharynx and nasopharynx. *Int J Radiat Oncol Biol Phys* 2008;**72**:1119–27.
18. Nguyen NP, Frank C, Moltz CC, Vos P, Smith HJ, Nguyen PD, et al. Analysis of factors influencing aspiration risk following chemoradiation for oropharyngeal cancer. *Br J Radiol* 2009;**82**:675–80.
19. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;**350**:1937–44.
20. Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. *Cancer* 1993;**71**:452–6.