Clinical Implications of Tumor Volume in Patients with the Base of Tongue Cancer Treated with Definitive Intensity-Modulated Radiotherapy Technique

Abstract

Purpose: To investigate the impact of tumor volume in patients with the base of tongue (BOT) cancer treated with definitive intensity-modulated radiotherapy technique (IMRT).

Materials and Methods: From 2003 to 2009, 35 patients with stage II-IV squamous cell carcinoma of the (BOT) cancer receiving organ preservation scheme were enrolled in this retrospective analysis. Radiotherapy was performed using a sequential IMRT. All patients received 1.8 Gy daily up to a median total dose of 70.2 Gy to gross tumors and metastatic lymph nodes, whereas the area harboring microscopic disease was prescribed with a median dose of 50.4 Gy. Twenty-four patients had concurrent chemotherapy. The regimen consisted of cisplatin (80–100 mg/m2 on Days 1, 22, 43). Primary tumor volume measurement was derived using separate simulation images for the pretreatment gross tumor volume (pGTV) and the interval gross tumor volume (iGTV).

Results: With a median follow-up duration of 18 months, 24 patients (68.5 %) were found to have locoregional failures. The 2-year cause-specific survival was for all patients was 24% and this could be split into 25% for stage II-III disease, and 18% for stage IV disease (p=0.29). The 2-year primary relapse-free survival (PRFS) was 35 % for patients with T2-T3 disease, and the curve dropped to zero for patients with T4 disease (p=0.01). The pGTV value ranged from 8.1 to 165mL (median, 34.6 mL), whereas the iGTV ranged from 3.8 to 79.3 mL (median, 19.4 mL)..Multivariate analysis showed that there were two predictors for the PRFS: pGTV $\geqq$ 20ml (p=0.02, hazard ratio= 5.87, 95% CI 1.29-26.72) and volume reduction rate (VRR) < 0.4 (p = 0.002, hazard ratio 4.33, 95% CI 1.71~10.99).

Conclusions: This preliminary study shows that IMRT outcome in the BOT cancer patients was unsatisfactory. To optimize the treatment result, a dose-escalation scheme or combined

surgery should be considered for large pretreatment tumor burden or a VRR less than 0.4.

Keywords: Base of tongue cancer, Intensity-modulated radiotherapy technique, Prognostic factor, Tumor volume.

Introduction

Traditionally, cancer of the base of the tongue (BOT) is classified as orophayngeal cancer. Earlier, there were some debates about the treatment of choice for this aggressive tumor. Generally, two major treatment options are usually recommended. One is surgery with or without adjuvant therapy; the other is organ sparing scheme using radiotherapy (RT) or concurrent chemoradiotherapy (CCRT). There were two large retrospective studies investigating the treatment outcome with organ sparing scheme [7, 15]. One of the two studies reported a comparable survival compared with previous surgical series [15], but the results seemed inferior than the RT outcome reported in several tonsillar cancer studies [2, 5, 6, 11, 14]. Because organ sparing scheme in oropharyngeal cancer patients has become one of the treatment of choice [14, 15], many physicians considered that resection of the large amount of oropharyngeal structures might endanger speech and swallowing function with subsequent jeopardizing patient's quality of life. Recently, the treatment option for oropharngeal cancer has shifted more toward organ preservation scheme with a popularity of intensity modulated radiotherapy technique (IMRT) or CCRT.

In our previous studies investigating the efficacy of organ sparing scheme in patients with tonsillar cancer [3, 13], a higher local recurrent rate was observed when compared to other western reports [2, 5, 6, 11]. One plausible reason for the poor RT outcome might be attributed to the lower prevalence of human papillomavirus (HPV)–related oropharyngeal cancer in Asia [4, 12]. For patients with the BOT cancer, a clinical investigation is also required to compare their outcome with the tonsillar analogue. In addition, a comprehensive analysis for this patient cohort is important when determining a better patient selection or performing a more aggressive combined modality treatment.

Tumor burden is a well known prognostic factor for head and neck patient treated by RT [17, 19]. The aim of this retrospective study was to investigate the volumetric impact on IMRT treatment outcome in patients with the BOT cancer. Furthermore, tumor volume

reduction rate (VRR) during RT has been reported to be a predictor of RT outcome for lung and rectal cancers [10, 18]. From the radiobiologic point of view, VRR during irradiation might relate to many factors, such as intrinsic radiosensitivity, tumor kinetics, capacity for tumor repopulation, and proportion of normal tissue in the tumor. When assessing local control by RT, using a single biologic model to represent the final treatment outcome might be problematic. Thus, the value of VRR is more important in definitive RT or CCRT for head and neck cancer because surgical resection is not always planned after treatment. To test the prognostic value of VRR in the BOT cancer during RT, the VRR was also analyzed when determining more appropriate patient selection criteria for salvage treatment or a dose escalation scheme.

Materials and methods

Patients

Between January 2003 to December 2009, 35 patients with stage II-IV squamous cell carcinoma of BOT patients, who were completed their allocated IMRT course for organ preservation scheme at China Medical University Hospital, were included in this retrospective study. All patients were staged after comprehensive physical examination, laryngoscopy, tumor biopsy, chest radiograph, computed tomography (CT) of the neck, abdominal ultrasonography and bone scan. None had distant metastasis after initial survey. There was no intended combined surgery following definitive RT.

The age of the patients ranged from 39 to 77 years with a median of 55 years. The men (n = 33) outnumbered the women (n = 2). The sites of tumor involvement were mainly based on the findings of laryngoscopy and all of the involved sites were recorded. For tumors involving both the BOT and the mobile tongue, the origins were determined by the amount of tumor burden at two sites. Neck lymph nodes were considered pathologic when matching any one of two criteria: 1) the shortest axis is larger than 0.8 cm; 2) multiple small lymph nodes

were in clusters. The patient characteristics and distribution of TNM classification are listed in Tables 1. The staging system was according to American Joint Committee on Cancer (AJCC) 6th edition staging system.

Treatment

A sequential intensity-modulated technique (IMRT) was given to all patients. They received 1.8 Gy daily up to a total dose of 68.4 to 72.0 Gy (median 70.2 Gy). The gross tumor volume (GTV) included the primary tumor and involved lymph nodes of more than 1-cm in diameter on CT imaging. The clinical target volume (CTV) modeled regions were considered two regions of different risks. The CTV1 encompassed the GTV and the regions adjacent to the gross tumor. The CTV2 consisted of ipsilateral or contralateral elective nodal regions at risk of harboring microscopic tumor. The planning target volume (PTV) consisted of a 3-mm margin in all directions around the CTV. The dose delivered to the CTV1/CTV2 during the first course was 50.4 Gy (1.8 Gy x 28 Fr) and the CTV1 was boosted a further 19.8 Gy (1.8 Gy x 11 Fr) during the second course. Thus, the cumulative dose to the CTV1/CTV2 was 70.2 Gy/50.4 Gy, respectively. The RT duration for all patients ranged from 43 to 77 days (median 56 days).

Twenty-four patients (68.6 %) received concurrent chemotherapy. The regimen consisted of cisplatin (80–100 mg/m2 on Day 1, 22, 43), as described in the Intergroup study [1].

Target volume delineation

Pre-treatment contrast-enhanced head and neck CT were performed in all patients. CT simulation was done with non-enhanced CT image with 3mm slice from orbital bone to 2 cm below Louis' angle. We co-registered the pre-treatment contrast-enhanced CT image and non-contrast CT simulation image for target volume delineation.

Generally, at least two radiation oncologists delineated the pretreatment primary gross tumor volume (pGTV). After 20 fractions of the first IMRT course, all patients underwent an adaptive CT simulation. Interval primary gross tumor volume (iGTV) was defined as the

residual primary tumor volume which was contoured in the adaptive image. The iGTVs were also determined with the same methods. The values of the pGTV and the iGTV were calculated automatically by the planning system (Eclipse Version 8.0). When the values varied by less than 10 %, an average of two readings was used as the measured volume. When the variation exceeded 10 %, another contouring and measurement was made for the correction of the biases. The detail of tumor volume definition was reported in our previous study [1]. Volume reduction rate (VRR) were calculated by the equation [VRR = (pGTV - iGTV) / pGTV] as described by our preceding study [19].

Follow-up

After the completion of the treatment, all patients were followed up every 1 to 2 month during the first 2 years, then every 3 to 4 months thereafter. Physical examination and laryngoscopic exam were performed during each follow-up examination and a CT scan of the neck was done every 4 to 6 months during the first 2 years. For the patients who survived, the follow-up period ranged from 4 to 81 months (median 13 months). The definition of local failure was based on the results of either the laryngoscopy or CT scan of the neck, or both. When the patient had persistent tumor or locoregional recurrence following initial complete remission, salvage surgery was suggested when technically feasible and the patient's condition allowed it.

Statistical analysis

Cause-specific survival (CSS), local relapse-free survival (LRFS) and primary relapse-free survival (PRFS) were calculated using the Kaplan-Meier method. Salvage of the recurrences was not taken into account in the evaluation of LRFS or PRFS. Significance levels between the curves were calculated using the log-rank test. Multivariate analysis was performed using Cox's proportional hazards model. Student's t test was used to assess the statistical significance of volumetric parameters between primary relapse and primary relapse-free groups. A p-value of less than 0.05 was considered statistically significant. All

calculations were performed with SPSS 13.0 for Windows (SPSS Inc, Chicago, IL, USA). Statistical significance was determined as $p < 0.05$, two-tailed.

Results

Complete remission was observed in 16 patients (45.7 %) when the treatment response was assessed at one month after treatment. With a median follow-up duration of 18 months, 7 patients were alive without documented recurrent disease. Three patients experienced locoregional relapse and were still alive after salvage or palliative treatment, one of them was observed to have lung metastsis. Eighteen patients had died of cancer (6 in primary relapse; 12 in both primary and neck lymph node relapse). Four patients died of complication without evidence of recurrent cancer. Three patients died due a metachronous or synchronous secondary cancer without tumor relapse (2 in hepatocellular carcinoma; 1 in esophageal cancer). Among the 21 patients with recurrent locoregional diseases, 7 have developed primary tumor relapse, 1 had isolated neck LN recurrence and 13 experienced both events. The outcome of all patients is listed in Table 2.

The 2-year CSS for all patients was 24% and this could be split into 25% for stage II-III disease, and 18% for stage IV disease (p=0.29). The 2-year LRFS was 30 % for patients with stage II-III disease, and 9 % for stage IV disease (p=0.13). The 2-year PRFS was 35 % for patients with T2-T3 disease, and the curve dropped to zero for patients with T4 disease (p=0.01), as depicted in Figure 1.

The pGTV value ranged from 8.1 to 165mL (mean, 47.1 mL; median, 34.6 mL), whereas the iGTV ranged from 3.8 to 79.3 mL (mean, 27.9 mL; median, 19.4 mL). The VRR value ranged from -0.18 to 0.64 (mean, 0.39; median, 0.41). The distribution of tumor volume and VRR respect to T stage is listed in Table 3. The correlation of volumetric parameters between primary failure and primary relapse-free groups is given in Table 4. Tumor volume changes according to primary relapse, were as followings: the mean pGTV in relapse-free patients was

31.73 mL(range, 8 to 73 mL) and , in patient who had primary relapse, 56.14 mL (range, 13-165 mL) (p=0.06). The mean iGTV in relapse-free patients was 15.1 mL (range, 3.8 to 37 mL) and, in patient who had primary relapse, 35.5 ml (range, 10 to 79mL) (p= 0.006). The mean VRR in relapse-free patients was 0.51 (range 0.28~0.6) and, in patients with relapse, 0.32 (range, -0.18~0.64) (p=0.008).

The impact of the tumors and the treatment-related parameters on the CSS and the PRFS were analyzed by univariate and multivariate analysis, and the results are presented in Table 5. Multivariate analysis showed two prognostic factors for the CSS: pGTV $\geqq$ 20 mL (p = 0.000, hazard ratio= 16.83, 95% CI 3.5-75.1), VRR < 0.3 (p = 0.000, hazard ratio= 10, 95% CI 3.1–31.3. There were two predictors for the PRFS: Multivariate analysis showed that there were two predictors for the PRFS: pGTV $\geqq$ 20ml (p=0.02, hazard ratio= 5.87, 95% CI 1.29-26.72) and a VRR < 0.4 (p = 0.002, hazard ratio 4.33, 95% CI 1.71~10.99). The results were not significant when the cutoff tumor volume or VRR was adjusted to other cutoff values. Figures 2 and 3 depict the correlation of the PRFS curves with the pGTV and VRR. The 2-year PRFS for pGTV < 20 mL and pGTV $\geqq$ 20 mL were 77 % and 8.7 % (p=0.01), whereas the curves for VRR > 0.4 and VRR $\geqq$ 0.4 were 37 % and 6 % (p= 0.001).

Discussion

There was a rarity of the available IMRT studies exploring the treatment outcome confining a single anatomic site of the BOT. Most reports used a pooling of data from all oropharyngeal structures, including tonsillar fossa, soft palate and pharyngeal wall. To the best of our knowledge, this study is the first Taiwanese investigation to explore the IMRT outcome in patients with the BOT cancer. Also, this work is the first report examing the impact of tumor volume on treatment out come in this cancer. When stratifying the stage and the volumetric data which were reported in our previous studies [13, 19], the treatment outcome was unsatisfactory compared to the tonsillar analogue. Thus, further optimization of

treatment modalities is required if the patient was planned to receive organ preservation scheme.

In Taiwan, the prevalence of HPV–related oropharyngeal cancers was less than 20 %, which was far lower than that in the western countries [4]. Perhaps, this might be a plausible explanation for the inferior outcome in our patients with the BOT cancer. However, it will be essential to further recognize the reasons for the substantial difference of the survival curves between the two cancers because the same RT strategy was taken in treating the tonsillar and the BOT cancer. To answer the question, a molecular study is ongoing in our hospital to identify the biomarkers other than HPV for the different oropharyngeal cancers.

Based on the results of our preliminary study, more efforts should be taken for circumventing the higher local failures. To achieve this goal, there are several feasible approaches. First, the median overall treatment duration was relatively longer because more fraction numbers were used in the sequential IMRT compared with that in the simultaneous integrated boost IMRT [2, 5, 6, 11]. Thus, it is essential to shorten the overall treatment time by using a large fraction size. Second, more extensive use of CCRT is recommended for this aggressive cancer because a phase III trial demonstrated the superiority of combined modality [1].

In addition, a planned combined surgery or a dose escalation scheme should be considered in those with large pGTV or small VRR. In particular, this study used a volumetric data that derived from the BOT cancer. Despite the fact that pretreatment tumor volume can be a predictive factor is not novel, treatment results might be optimized if volumetric data was used to supplement the clinical stage. Because of diversity in the radiosensitivity between tumors of different origins, the clinical implication of volumetric data seems to be limited if the studied group includes heterogeneous tumor sites. In our previous study [19], the large pretreatment tumor volume and the VRR less than 0.5 were two poor outcome predictors for local control in patients with the tonsillar and the hypopharyngeal cancer treated in the IMRT

era. This study demonstrated a similar finding that those with pGTVs more than 20 mL or VRRs less than 0.4 did poor in PRFS. Thus, they should be considered for a salvage operation or a dose-escalation scheme.

Cancers of the BOT tend to be infiltrative and more extensive than image or endoscopy suggested. This makes it difficult for the surgeon to ensure if the resected tissue encompasses all microscopic tumors [7]. Nonetheless, Robertson et al. conducted a phase III trial to investigate the outcome in patients with advanced tongue and mouth floor cancers, treated by surgery plus postoperative RT or definitive RT [16]. Their study was closed prematurely because the authors found that the survival was substantially improved in the surgery plus adjuvant RT arm after a median follow-up of 23 months. Accordingly, radical surgery plus postoperative RT/ CCRT is probably an alternative way to achieve a better locoregional control or survival in selective patients with the BOT cancer as the similar conclusion shown in an another phase III trial [8].

Furthermore, interstitial brachytherapy is another feasible way to improve local control. It can be used to be a boost treatment combined with external beam radiation or as a single modality for early tumors. For unresectable BOT cancers, Karakoyun-Celik Omur et al. demonstrated a boost interstitial brachytherapy could achieve a 5-year local control and overall survival of 62% and 78% [9]. In their study, 122 patients were treated with a median external beam dose of 61.2Gy following by a brachytherapy boost of a median implant dose of 17.4 Gy.

There were several limitations in our study. First, the patient number was quite small. Second, the follow-up duration was not rather long. Because both factors could contribute statistical bias in our study, a larger cohort with sufficient follow-up duration is required to elucidate comprehensive outcome for the BOT cancer patients. Finally, the contouring uncertainties might also affect the result of the VRRs, particularly in the interval GTV derived from the adaptive image. The variations can be reduced with the use of contrast-enhanced CT

during simulation.

In conclusion, our preliminary report showed that the IMRT outcome in the BOT cancer patients was unsatisfactory. In those with pGTVs $\geqq$ 20 mL or VRRs < 0.4, a planned combined surgery or a more aggressive RT scheme should be considered for optimizing the treatment outcome in this highly aggressive cancer.

Figures Legends

Figure 1. Primary tumor relapse-free survival curves according to T-stage for all patients.

Figure 2. Primary tumor relapse-free survival curves according to pretreatment GTV volume for all patients (pGTV < 20ml vs. ≧ 20mL).

Figure 3. Primary tumor relapse-free survival curves according to volume reduction rate (VRR) for all patients (VRR ≧ 0.4 vs. VRR < 0.4)

Tables

Fig. 1 PRFS-T stage

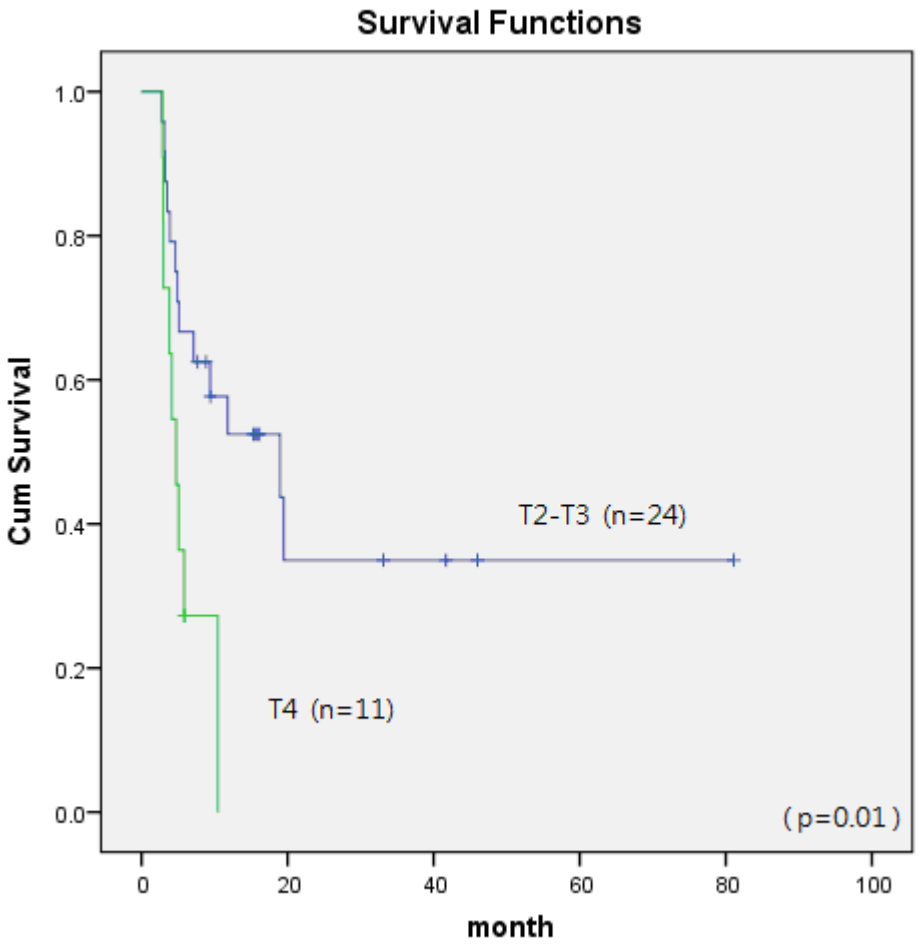


Fig. 2 PRFS_pGTV

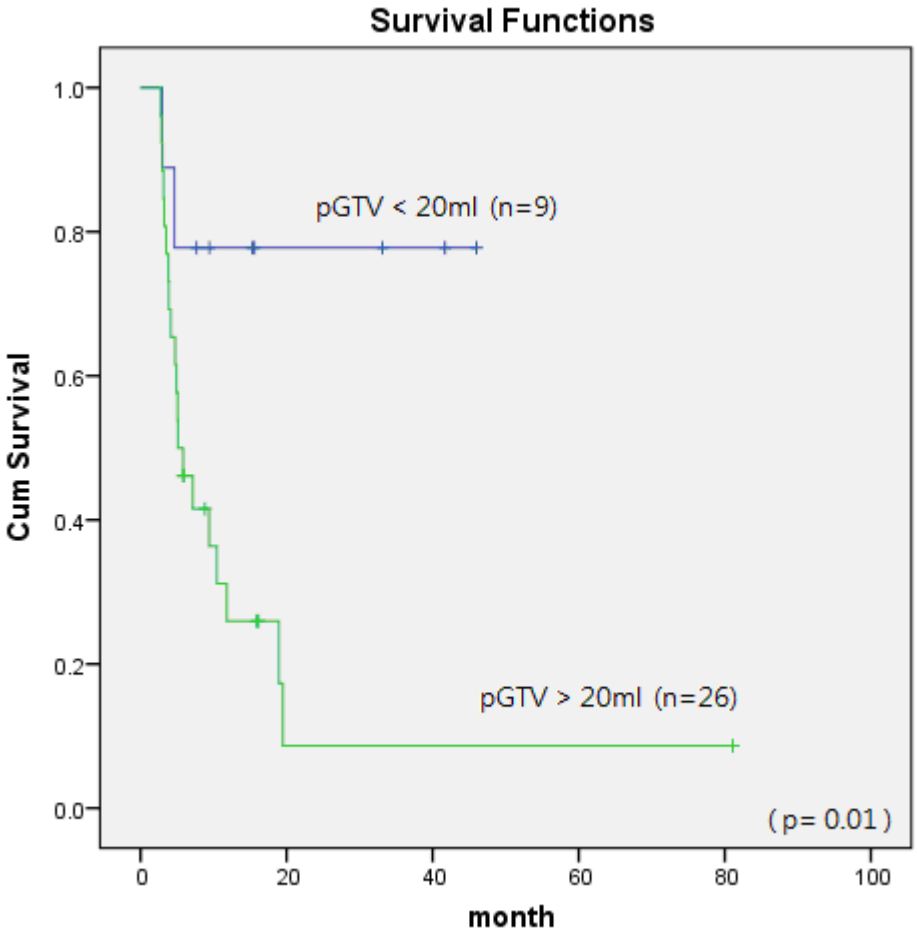
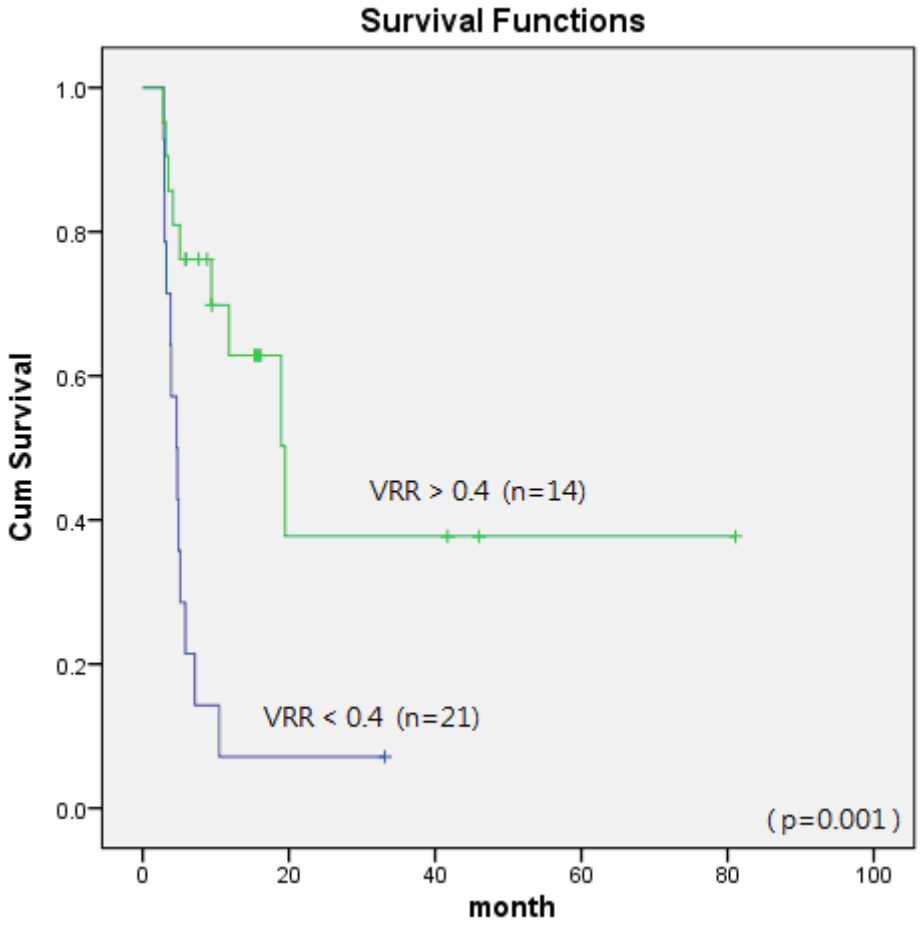


Fig. 3 PRFS_VRR



Tables

Table 1. Patient characteristics in base of tongue cancer (Total, 35 patient)

Characteristic	Value
Age (years)	39-77 (median, 55)
Sex	Male 33 , Female 2
Pathology	
W-D/M-D squamous cell carcinoma	15
P-D squamous cell carcinoma	3
Unclassified	10
Others	7
AJCC Stage	II: 3 III: 4 IVa: 25 IVb: 3
Performous status	
ECOG 0-1 / 2	33 / 2
Tracheostomy	
Negative / positive	28 / 7
Radiation dose (Gy)	68.4 to 74.4 (median, 70.2)
Treatment duration	43 to 77 (median, 56)
Concurrent chemotherapy	
Yes	24
No	11
Follow up (months)	4-81 (median, 18)

Abbreviation: W-D = well-differentiated; M-D =moderately-differentiated; P-D = poorly-differentiated; AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group.

Table 2 Patient outcome in base of tongue cancer

Outcome	Patient number
Alive without evidence of recurrence	7
Alive with evidence of recurrence	3
Primary relapse and lung metastasis	1
Neck lymph node relapse	1
Primary + neck lymph node relapse	1
Died of cancer	18
Primary relapse	6
Primary and neck lymph node relapse	12
Died of complication without evidence of recurrent cancer	4
Died of metachronous or synchrounous second cancer without evidence of recurrent disease	3

Table 3. primary tumor volume and volume reduction rate vs. T stage

	No.	Mean pGTV (ml)	Mean iGTV (ml)	Mean VRR	No. of VRR			
					> 0.6	> 0.5	> 0.4	> 0.3
ALL	35	47.1 (8.1~165)	27.9 (3.8~79.3)	0.39 (-0.18~0.64)	4	13	21	27
T2	16	28.5 (8.1~68.6)	15.7 (4.6~33.9)	0.43 (0.16~0.60)	2	7	11	14
T3	8	54.8 (18.2~125.9)	28.5 (9.5~73.5)	0.47 (0.3~0.61)	1	4	6	8
T4	11	70.2 (16.4~165.3)	46.3 (12.5~79.3)	0.26 (-0.18~0.64)	1	2	4	5

Abbreviations: pGTV = pretreatment gross tumor volume; iGTV = interval gross tumor volume; VRR = volume reduction rate.

Table 4. Correlation between tumor volume parameters and primary tumor relapse

	Primary tumor relapse (+) (n=22)	Primary tumor relapse (-) (n=13)	p-value
Mean pGTV(ml) ± SD	56.14 ± 39.9	31.73 ± 22.69	0.06
Mean iGTV(ml) ± SD	35.51 ± 22.78	15.09 ± 10.32	0.006*
Mean VRR ± SD	0.32 ± 0.22	0.51 ± 0.09	0.008*

Abbreviations: pGTV = pretreatment gross tumor volume; iGTV = interval gross tumor volume; VRR = volume reduction rate; SD = standard deviation.

Table 5. Result of univariate and multivariate analysis for cause-specific survival and primary tumor relapse-free survival

Variables	CSS Univariate p-value	CSS Multivariate p-value	PRFS Univariate p-value	PRFS Multivariate p-value
Age < 50 vs. ≧ 50	0.59	0.36	0.04	0.41
T2-T3 vs. T4	0.008	0.73	0.01	0.46
Stage II-III vs. Stage IV	0.29	0.67	0.22	0.79
N0 vs. N1-3	0.70	0.31	0.7	0.23
Treatment duration < 60 days vs. ≧ 60 days	0.44	0.93	0.07	0.92
Smoking (+) vs. (-)	0.03	0.06	0.77	0.80
pGTV < 30mL vs. ≧ 30mL	0.07	0.34	0.17	0.64
pGTV < 25ml vs. ≧ 25mL	0.006	0.05	0.02	0.66
pGTV< 20ml vs. ≧ 20mL	0.13	0.02	0.01	0.02
pGTV < 15 vs. ≧ 15 mL	0.52	0.97	0.21	0.68
VRR ≧ 0.6 vs. VRR < 0.6	0.36	0.88	0.38	0.7
VRR ≧ 0.5 vs. VRR < 0.5	0.57	0.91	0.01	0.07
VRR ≧ 0.4 vs. VRR < 0.4	0.04	0.44	0.001	0.002
VRR ≧ 0.3 vs. VRR < 0.3	0.04	0.000	0.019	0.18
VRR ≧ 0.2 vs. VRR < 0.2	0.12	0.78	0.04	0.01

Abbreviations: CSS = cause-specific survival; PRFS = primary tumor relapse-free survival; pGTV = pretreatment gross tumor volume; VRR = volume reduction rate.

References

1. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92–98.
2. Chao KS, Ozyigit G, Blanco AL, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: impact of tumor volume. Int J Radiat Oncol Biol Phys 2004; 59:43–50.
3. Chen SW**,** Yang SN, Liang JA, et al. Prognostic impact of tumor Volume in Patients with Stage III-IVA hypopharyngeal cancer without bulky lymph nodes treated with definitive concurrent chemoradiotherapy. Head Neck Journal 2009: 31; 709-716.
4. Chien CY, Su CY, Fang FM, et al. Lower prevalence but favorable survival for human papillomavirus-related squamous cell carcinoma of tonsil in Taiwan. Oral Oncol 2008;44:174–179.
5. de Arruda FF, Puri DR, Zhung J, et al. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: The Memorial Sloan-Kettering Cancer experience. Int J Radiat Oncol Biol Phys 2006;64:363–373.
6. Huang K, Xia P, Chuang C, et al. Intensity-modulated chemoradiation for treatment of stage III and IV oropharyngeal carcinoma: The University of California-San Francisco experience. Cancer 2008;113:497–507.
7. Jaulerry C, Rodriguez J, Brunin F, et al. Results of radiation therapy in carcinoma of the base of the tongue. The Curie Institute experience with about 166 cases. Cancer. 1991 Mar 15;67(6):1532-8.
8. Jay S. Cooper, Thomas F, et al. RTOG9501. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-44.
9. Karakoyun-Celik O, Norris CM, Tishler R, et al. Definitive radiotherapy with interstitial

implant boost for squamous cell carcinoma of the tongue base. Head Neck 27: 353–361, 2005

10. Kim YH, Kim DY, Kim TH, et al. Usefulness of magnetic resonance volumetric evaluation in predicting response to preoperative concurrent chemoradiotherapy in patients with resectable rectal cancer. Int J Radiat Oncol Biol Phys 2005;62:761–768.
11. Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. Int J Radiat Oncol Biol Phys 2007;69:459–468.
12. Li W, Tran N, Lee CS, et al. New evidence for geographic variation in the role of human papillomavirus in tonsillar carcinogenesis. Pathology 2007;39:217–222.
13. Liao CY, Yang SN, Liang JA, Tsai MH, Chen SW, Lin FJ. Value of computed tomography-based tumor volume as a predictor of local control in oropharyngeal cancer after treatment of definitive radiotherapy. Therapeutic Radiology and Oncology 2009;16 (1):15-24.
14. Mendenhall WM, Amdur RJ, Stringer SP, et al . Radiation therapy for squamous cell carcinoma of the tonsillar Region: A preferred alternative to surgery? J Clin Oncol 2000: 18; 2219-2225.
15. Mendenhall WM, Stringer SP, Amdur RJ, et al. Is Radiation Therapy a Preferred Alternative to Surgery for Squamous Cell Carcinoma of the Base of Tongue? J Clin Oncol. 2000 Oct 1;18(19):3452-3.
16. Robertson AG, Souter DS, Paul J, et al. Early closure of a randomized trial: surgery and postoperative radiotherapy versus radiotherapy in the management of intra-oral tumours. Clin Oncol 1998;10:139-40.
17. Studer G, Lutolf UM, El-Bassiouni M, et al. Volumetric staging is superior to TNM and AJCC staging in predicting outcome of head and neck cancer treated with IMRT. Acta Oncol 2007;46: 386–394.

18. Werner-Wasik M, Xiao Y, Pequignot E, et al. Assessment of lung cancer response after nonoperative therapy: Tumor diameter, bidimensional product, and volume. A serial CT scan based study. Int J Radiat Oncol Biol Phys 2001;51:56–61.

19. Yang SN, Liao CY, Chen SW, Liang JA, et al. Clinical implications of the tumor volume reduction rate in head and neck cancer during definitive intensity modulated radiotheraphy for organ preservation. Int J Rad Oncol Biol Phys 2010 (in press).

舌根癌病人之腫瘤體積於強度調控放射治療的預後因子研究

摘要

目的: 探討舌根癌病人的**腫瘤體積對於強度調控放射治療**預後的影響。

材料與方法: 回溯性分析從 2003 年到 2009 年期間， 35 位確診為臨床二至四期鱗狀上皮癌舌根癌且接受器官保留治療病人的病例紀錄。所有病人皆完成兩階段強度調控式放射線治療，每天接受之**放射**劑量為 1.8 Gy，原發腫瘤與轉移性淋巴結接受的總劑量之中位值為 70.2 Gy，預防性頸部淋巴的劑量之中位值為 50.4 Gy。其中的 24 位病人接受合併 cisplatin之同步化學治療（cisplatin 80-100mg/m^2，放療開始的第 1、22、43 天）。原發腫瘤體積之測量與計算分別取自**放射**治療前及治療期中之模擬攝影影像。

結果: 經過中位值 18 個月的追蹤時間， 24 位病人(68.5 %)被發現有原發腫瘤或頸部淋巴之局部復發。所有病人之兩年癌症相關存活率為 24 %，其中第二至三期病人的癌症相關存活率為 25 %，第四期病人之癌症相關存活率為 9 %(p=0.13)。另T2-T3 腫瘤的兩年原發腫瘤無復發率為 35 %，而T4 腫瘤的則降至 0 % (p=0.01)。原發腫瘤體積之中位值為 34.6 mL(範圍， 8.0 至 165 mL)，而治療中之原發腫瘤體積之中位值為 9.4 mL(範圍， 3.8 至 79.3 mL)。多變數分析發現原發腫瘤復發之不良預後因子為原發腫瘤體積大於 20 mL (p=0.005，勝算比 5.87，95 % 信賴區間 1.29-26.7) 與放療期中腫瘤體積降低比率小於 0.4 (p=0.002，勝算比 3.74，95 %信賴區間 1.68~9.73)。

結論:本研究報告顯示強度調控治療對於施行器官保留術之舌根癌病人的治療成效並不理想，對於原發腫瘤體積大於20 mL或放療期中腫瘤體積降低比率小於0.4的病人，必須考慮以更積極的治療方式來提高局部腫瘤的控制率，如提高局部放射治療劑量或是合併手術切除。

關鍵字: 舌根癌，**強度調控放射治療**，預後因子，腫瘤體積。

A 審評審委員意見：

1. 文中沒有把腫瘤細胞的 differentiation 列出。Tongue base cancer 的分化應偏向 poorly differentiated cancer、如 differentiation 為 well differentiation 偏多者則可能是 tongue cancer 而非 tongue base cancer。

2. 文中腫瘤診斷時所使用的影像是採用電腦斷層而非核磁共振、因此在腫瘤的初步判定侵犯範圍時可能會有所失真（T 會 understaging）、甚至可能為舌癌而誤判為 tongue base cancer。以上二點為 reviewer 所顧慮的、如初步診斷不正確，其結論常會誤導讀者。

3. Reviewer 懷疑診斷不正確的另一個原因是 tongue base cancer 其存活介於 hypopharyngeal cancer 與 laryngeal cancer 的 survival curve 兩者間。但文中的 tongue base cancer patient 存活過差、是否有一部份是 tongue cancer 沒有接受手術治療因誤判為 tongue base cancer、而祇接受 CCRT 的治療。

4. 文中的病人癒後過差、但不應導出應合併接受手術一途。此建議使 reviewer 更相信此文章的病人除了部份 tongue base cancer 外也合併一些 tongue cancer 侵犯 tongue base 的病人。建議應詳細 review 病歷、

如 tongue palpation 的記載等、把 tongue cancer 的病人刪除後，結果應不一樣。

5. 如作者把 tongue cancer 的病人刪除後仍然得到相同結論，則 reviewer 相信在劃定 GTV 等的範圍時有誤差(因 T understaging)才會有此結論，請作者小心、因所得結論與一般 tongue base cancer 病人治療的結果不一樣。

B 審評審委員意見：

總評：This article which pointed out the impact of pretreatment tumor volume and volume reduction rate in patients with base of tongue cancer treated with definitive IMRT is important for clinical use.

分論：本篇創意及研究嚴謹度非常優異，但於討論部份建議依研究結果更深入討論。

1. 35 位病人中有 24 位接受合併化學治療，另 11 位則否。合併化學治療對 VRR, CSS, PRFS 是否有影響？

2. Discussion 依 results 的結果做引申及討論。

但第三段提及 ”Thus, it is essential to shorten the overall treatment time…..” 與 Table 5 的結果並不符合。

“Second, more extensive use of CCRT is recommended….”，但本研究中並無合併化學治療是否優於單獨放射治療的分析。

3. 本篇主旨在 ”volume” 與 ”treatment outcome” 的關連。Discussion 中，應強化此部分的討論。如：增加與其他同樣探討 volume 與 treatment outcome 之論文的討論（ref. 18）。

助理編輯意見：

1. 第 19 頁 Table 2，請於 2 後面加一句點；另請將表二 Patient number 之數據對齊。

2. Table 3, 5 請刪除縱線，如同 Table 2 即可。

3. 以下為參考文獻頁格式之問題，請按稿約要求格式修改：

1) 第 23-25 頁之參考文獻，於共同作者 et al. 後面加一冒號區隔。

2) 文獻第 7, 8 篇，請將起迄頁數完整標示，如 1532-8，應為 1532-1538。

3) 文獻第 7, 15 篇，請將期刊名稱後面之句點刪除。

4) 文獻第 9 篇，請將年代移至卷數之前。

5) 文獻第 13 篇，期刊名應縮寫，期刊名稱前多空了一空格，請刪除。

4. 請將中文摘要頁內之半型括弧改為全型括弧。

5. 中文摘要最末行，請將關鍵字改為關鍵詞。

6. 文稿首頁，通訊地址地方，除有地址及醫院名外，尚遺漏科別名稱。