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ORIGINAL ARTICLE

Tumour Volume as a Predictor of Treatment Success in Patients with Laryngeal Cancer Treated with Primary Chemoradiotherapy

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ABSTRACT

Objectives: *To evaluate the prognostic significance of pretreatment tumour volume in predicting local control, with a functioning larynx, in patients with laryngeal cancer treated with primary chemoradiation.*

Methods: *Thirty-two patients with American Joint Committee on Cancer stage II-IV squamous cell carcinoma of the larynx were retrospectively reviewed. All patients received concurrent chemoradiation between 2000 and 2007. Tumour volumes were contoured and calculated on computed tomography simulation scans. The median follow-up was 2.1 years. The median radiotherapy dose was 74.4 Gy.*

Results: *Of the 32 patients, 20 had supraglottic tumours, 11 had glottic tumours, and 1 had a subglottic tumour. For the entire cohort of patients, the 5-year overall survival rate was 45% and the 5-year local control rate for patients with a functional larynx was 66%. In all, 80% of patients with supraglottic tumour volumes of ≤12 cm³ achieved local control with a functioning larynx compared with only 44% of patients with supraglottic tumour volumes of >12 cm³ (p = 0.0268). For glottic cancers, it was not possible to discern a relationship between tumour volume and tumour control.*

Conclusions: *Pretreatment tumour volume of ≤12 cm³ predicted local control with a functioning larynx in patients with supraglottic squamous cell carcinoma treated with chemoradiation.*

Key Words: *Chemotherapy, adjuvant; Head and neck neoplasms; Radiotherapy; Treatment outcome; Tumor burden*

中文摘要

以腫瘤體積作為喉癌患者第一線放化療成功的預測指標

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目的：本研究針對接受化學放射治療為第一線治療的喉癌患者，評估以治療前的腫瘤體積作為預測局部控制和喉功能正常的預後預測指標的重要性。

方法：回顧分析按美國癌症聯合委員會標準診斷的II至IV期喉鱗狀細胞癌的32名患者。所有患者均於2000年至2007年期間同時接受化療與放療。在電腦斷層模擬掃描上勾畫腫瘤輪廓並計算體積。隨訪時間中位數為2.1年。放療劑量中位數為74.4 Gy。

結果：32名病人中，聲帶上部腫瘤佔20例、聲帶腫瘤佔11例，以及聲帶下部腫瘤佔1例。病人的五年總存活率為45%，腫瘤五年局部控制伴喉功能正常的比率為66%。所有病人中，聲帶上部腫瘤體積≤12 cm³，則腫瘤局部控制伴喉功能正常的比例可達80%；而聲帶上部腫瘤體積>12 cm³的則只有44%（p = 0.0268）。至於聲帶腫瘤的情況，則未能確定腫瘤體積與腫瘤控制的關係。

結論：接受放化療的聲帶上部鱗狀細胞癌患者中，腫瘤體積≤12 cm³可作為腫瘤局部控制伴喉功能正常的預測指標。

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INTRODUCTION

After the results of the Veterans Affairs Laryngeal Cancer trial[1] were published in 1991, the treatment of advanced squamous cell carcinoma (SCC) of the larynx evolved from an almost exclusive surgical approach to including the option of larynx preservation through primary chemoradiotherapy.[2,3] Larynx preservation offers a significant improvement in patients' quality of life over total laryngectomy, but selecting the most appropriate patients is critical to maintaining equivalent cancer control.[4]

At the University of Florida, Gainesville, FL, USA, using the tumour volume outcome studies by Mancuso et al[5] and Pameijer et al[6] as guides, only patients with low-volume advanced laryngeal SCC are treated with primary radiotherapy. These studies demonstrated that patients with large-volume tumours, as measured on their pretreatment computed tomography (CT) scan, had worse outcomes after primary radiotherapy than patients with small-volume tumours. The tumour volume cut-offs found to be significant in these studies were quite small (3.5 cm^3 for glottic and 6 cm^3 for supraglottic tumours). As patients in these studies were treated with radiotherapy alone and no chemotherapy, we hypothesised that adding concurrent chemotherapy might allow for an increase in the tumour volume that could be treated successfully with larynx-preservation therapy. We based this hypothesis on data showing improved local control with the addition of concurrent chemotherapy to radiotherapy.[7-9] The purpose of this study was to evaluate the prognostic significance of pretreatment tumour volume in predicting local control with a functioning larynx in patients with laryngeal cancers treated with concurrent chemoradiation.

METHODS

The records of 32 consecutive patients with SCC of the supraglottic, glottic, or subglottic larynx treated curatively with definitive chemoradiation at the University of Florida between March 2000 and November 2007 were retrospectively reviewed under an institutional review board–approved protocol. Tumour staging was based on guidelines of the American Joint Committee on Cancer, 6th edition.[10] Patients with node-negative T1 or T2 glottic tumours, any primary tumour of >30 cm^3, or who received induction chemotherapy were excluded.

Each patient underwent a pretreatment, contrast-enhanced CT scan of the head and neck with 3-mm slices. The pretreatment primary tumour was contoured retrospectively and a tumour volume was calculated using the Pinnacle 8.0M treatment planning system (Philips Medical Systems, Andover, MA, USA). A consensus volume was reached by two radiation oncologists for each patient.

All tumours were treated with radiation doses between 7320 and 7680 cGy. The median radiation dose was 7440 cGy. Patients were treated with hyperfractionated radiation (59%), conventional daily radiation (19%), or with the concomitant boost technique (22%). The median dose, fractionation scheme, and treatment time for patients with tumours >6 cm and those ≤6 cm were similar. Intensity-modulated radiation therapy was used to treat only 25% of the patient population. The remaining patients were treated with conventional fields. Of the 32 patients, 21 received weekly cisplatin of 30 mg/m^2 during radiation; the remaining patients were treated with either concurrent carboplatin or concurrent taxol with carboplatin. Two patients were treated with concurrent intra-arterial cisplatin chemotherapy as part of an experimental protocol.

Patients were followed up by a radiation oncologist indefinitely. Major treatment complications were recorded and graded using the Common Terminology Criteria for Adverse Events version 3.0. Local failure was defined as a persistence or regrowth of carcinoma involving the larynx following completion of radiotherapy. Regional failure was defined as a recurrence of disease within regional lymphatics in the absence of local recurrence. Distant recurrence was defined as the development of disease at a distant site or non-regional lymphatic site in the absence of loco-regional recurrence.

SAS and JMP software were utilised for all statistical computations (SAS Institute, Cary, NC, USA). Statistical analysis with regard to local control rates and preservation of laryngeal function was performed using a combination of Fisher's exact test (for nominal prognostic factors) and logistic regression (for continuous prognostic factors). The Kaplan-Meier product limit method provided estimates of overall survival and local control; significance levels between the curves were calculated using the log-rank test.[11]

RESULTS

Patient and Tumour Characteristics

The clinically significant characteristics of the patient

population are listed in Table 1. Overall, 23 men and 9 women were included in this study. The median age was 63 years. At presentation, 20 patients had supraglottic tumours, 11 had glottic tumours, and 1 had a subglottic tumour. Thirty-one patients had either stage III or IVA disease, while only one patient had stage II disease. The patient with stage II disease, who had T2 N0 disease, had a bulky subglottic laryngeal cancer and was treated with chemoradiation because of the attending physician's preference. The tumour and nodal stage distribution is listed in Table 1.

The median tumour volume was 10 cm^3 (range, 1-23 cm^3). Thyroid cartilage invasion was defined as visible tumour crossing the inner and outer table of the thyroid cartilage, and it was seen in four (13%) patients. Sixteen patients presented with vocal cord fixation. Only four patients had evidence of soft tissue invasion.

Overall Outcomes

The median follow-up time was 2.1 years for all patients and 5.6 years among survivors. Kaplan-Meier survival curves are shown in Figure 1. For the entire cohort of patients, the 5-year overall survival rate was 45% and the 5-year local control rate for patients with a functional larynx was 66%. The cause-specific survival rate at 5 years was 56%. Overall, six (19%) patients experienced a local failure, one of whom underwent successful salvage surgery and achieved long-term survival. Three patients experienced a regional nodal failure in the absence of local failure. None underwent salvage therapy. Four patients recurred with distant metastases.

Table 1. Patient and tumour characteristics (n=32).

Characteristic	No. (%) of patients*
Sex	
Male	23 (72%)
Female	9 (28%)
Primary site	
Glottis	11 (34%)
Supraglottis	20 (63%)
Subglottis	1 (3%)
T stage	
T1	-
T2	6 (19%)
T3	17 (53%)
T4	9 (28%)
N stage	
N0	19 (59%)
N1	0 (0%)
N2A/B	4 (13%)
N2C	6 (19%)
N3	3 (9%)
Median (range) tumour volume (cm^3)	10 (1-23)
Thyroid cartilage invasion	4 (13%)
Vocal cord fixation	16 (50%)
Soft tissue invasion	4 (13%)

* Unless otherwise stated.

Effect of Tumour Size on Outcomes

Each tumour site within the larynx was analysed separately and, for supraglottic cancers, patients with tumours of ≤12 cm^3 had local control with functional larynx rates at 5 years of 80% versus 44% for patients with tumours >12 cm^3, which was statistically significant (p = 0.0268; Figure 2). The tumour volume cut-off value was 12 cm^3 because it was the median tumour volume for supraglottic cancers. For glottic cancers, it was not possible to discern a relationship between tumour volume and tumour control. Using tumour volume of 6 cm^3 (the median tumour volume for

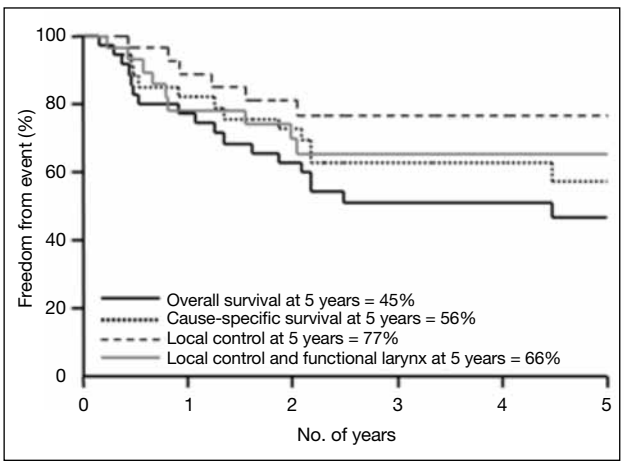

Figure 1. Overall survival, cause-specific survival, and local control at 5 years.

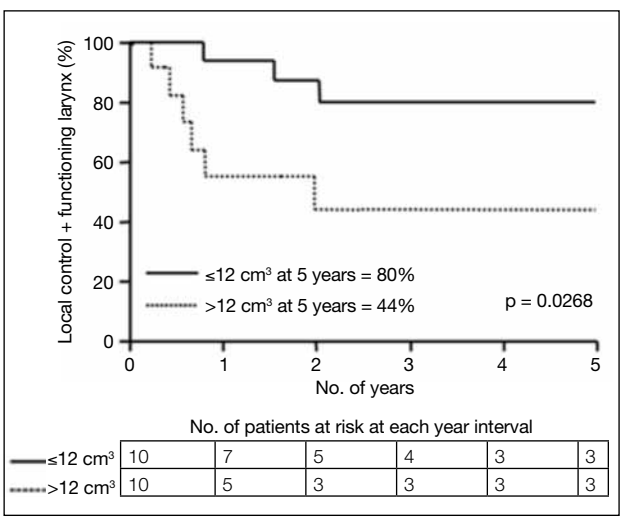

Figure 2. Local control with a functioning larynx stratified by tumour volume for supraglottic cancers.

glottis cancers) as the cut-off, there was no significant difference in the local control with functional larynx rates for glottic tumours (80% for tumours ≤6 cm^3 vs 83% for tumours >6 cm^3). Because of small numbers, a p value for this comparison could not be calculated.

Complications

Eight (25%) of 32 patients experienced at least one grade 3 to 5 complication. A total of nine grade 3 to 5 complications occurred in eight patients, making the total grade 3 to 5 complication rate of 28%. The details of each complication are shown in Table 2. Of the five patients who developed chondronecrosis of the larynx after treatment, two underwent total laryngectomy.

The grade 3 to 5 complication rate for patients who achieved local control was 27%. The grade 3 to 5 toxicity rate for patients who required total laryngectomy for local failure or radionecrosis was 25%. Grade 5 toxicity occurred in four (13%) patients. Three patients who died due to complications of treatment had locally controlled disease. One patient who failed locally in the larynx died of postoperative complications following salvage surgery.

DISCUSSION

This study examined the question of whether the primary tumour volume of laryngeal cancers affects the probability of local control with a functional larynx following definitive chemoradiotherapy. The results suggest that tumour volume for supraglottic tumours is likely to correlate with outcome following chemoradiotherapy. Patients with tumour sizes of >12 cm^3 were less likely to achieve meaningful local control and larynx preservation. Conversely, it was not possible to show a relationship between tumour volume and local control for glottic cancers.

This study follows several publications demonstrating that tumour volume, independent of stage, can predict outcomes in patients with laryngeal cancers confined to the glottis or supraglottis treated with radiotherapy alone.[12-15] Mancuso et al[5] showed that supraglottic cancers of >6 cm^3 had worse rates of local control with a functioning larynx following definitive radiation. Another similar study demonstrated that glottic cancers of >3.5 cm^3 had worse prognoses than smaller tumours when treated with definitive radiation.[6] Our hypothesis suggested that adding concurrent chemotherapy to primary radiotherapy allows larger-volume supraglottic tumours to be treated successfully with larynx-preserving therapy compared with radiotherapy alone.

Recently, two studies have been published demonstrating the role of primary tumour volume in predicting local control for patients with head and neck cancers treated with primary chemoradiotherapy. Strongin et al[16] determined that patients with oropharynx, larynx, and hypopharynx cancers with primary tumour volumes of ≥35 cm^3 versus patients with tumour volumes of <35 cm^3 had worse 5-year overall survival (41% vs 84%, $p < 0.001$) and progression-free survival (43% vs 71%, $p = 0.10$) following chemoradiation. Lok et al[17] determined that after chemoradiotherapy for oropharynx cancers, large primary gross tumour volumes predicted for local failure ($p < 0.0001$), worse overall survival ($p = 0.0003$), and distant metastasis following chemoradiotherapy ($p = 0.0008$). Both studies support

Table 2. Patient complications.*

Tumour size (cm^3)	Tumour site	Complication grade	Description of complication
8	Glottis	5	Radionecrosis of the larynx requiring tracheostomy; died of respiratory distress 1 year after completing therapy
11	Supraglottis	5	Neutropenia; died of sepsis 5 weeks after completing therapy
12	Supraglottis	4	Radionecrosis of the larynx requiring total laryngectomy
13	Supraglottis	3	Dysphagia requiring percutaneous endoscopic gastrostomy tube for >6 months
15	Supraglottis	4	Radionecrosis of the cricoid requiring hyperbaric oxygen
15	Supraglottis	5	Radionecrosis of the larynx requiring tracheostomy; died of aspiration pneumonia 2 years after completing therapy
16	Supraglottis	4	Radionecrosis of the larynx requiring total laryngectomy
21	Supraglottis	3	Chronic mandibular osteomyelitis requiring antibiotics
23	Supraglottis	5	Total laryngectomy for local failure; died from postoperative stroke and aspiration 6 months after completing therapy

* 25% of patients had grade 3-5 toxicity. Overall, the grade 3-5 complication rate was 28%. The grade 3-5 complication rate for patients who achieved local control was 27%. The grade 3-5 toxicity rate for patients who required total laryngectomy for local failure or radionecrosis was 25%. Grade 5 toxicity occurred in 4 (13%) patients including 1 patient who died after salvage surgery.

the hypothesis that primary tumour volume is an independent predictor of successes or failure following chemoradiation for head and neck cancers.

This study is limited by its retrospective nature. A small sample size and limited follow-up for each larynx subsite also reduced our ability to provide statistically relevant results for subgroup analysis, particularly for patients with glottic or subglottic cancers. Additionally, the reliability and accuracy of our measurements of tumour volume are inherently a source of potential error due to the subjective nature of defining the gross tumour volume. Finally, although one patient with T2 N0 subglottic cancer was included in this study, we do not suggest that all patients with T2 N0 subglottic cancers have locally advanced disease or that they should be treated with chemoradiation.

CONCLUSIONS

In patients with supraglottic carcinoma and a TNM stage greater than T2 N0, tumour volume may be a major consideration in treatment choice. Larynx preservation using radiation with concurrent chemotherapy with modern techniques and drugs may be inadequate if tumour size is large, particularly if >12 cm^3. Given this finding, tumour volumes should be considered when triaging patients for laryngectomy versus larynx-preserving treatment. However, these results need to be validated in a larger study. If chemoradiotherapy is delivered to patients with large tumour volumes, close follow-up is advised because of the higher local-regional failure and complication rates in this group.

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