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# Tumor volume as a predictor of survival in T3 glottic carcinoma: A novel approach to patient selection☆

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ABSTRACT

*Background:* The optimal treatment for T3 glottic cancers continues to be debated. Organ preservation has become the standard of care, but not all tumors respond equally. The purpose of this was to investigate the long-term survival outcomes of organ preservation protocols based on tumor volume.

*Methods:* A retrospective review of prospectively collected data from 1966 to 2016 was performed. Patients with T3 vocal cord cancer treated with radiation therapy (RT) at the University of Florida were included. Local control rates as well as survival rates were determined with a Kaplan Meier and Cox regression analysis. Survival was analyzed as a function of tumor volume and an optimal cut point was determined.

*Results:* 107/234 patients were included. 79% received RT and 21% chemo-RT. 5-year local control was 61.5% and 5-year disease specific survival was 79.3%. Tumor volume was a significant predictor of survival ($p = 0.007$). An optimal cut point for tumor volume was 2.5 cc. Patients with tumor volumes $\geq 2.5$ cc had significantly worse ($p < 0.05$) tumor control rates (100% vs. 70.4%).

*Conclusion:* Tumor volume is a significant predictor of survival outcomes in T3 vocal cord cancers, but will need external validation. Tumors < 2.5 cc have favorable outcomes. Those with higher volume tumors should be counselled appropriately and be considered for primary surgical management.

## Introduction

Advanced laryngeal cancer will affect over 4000 Americans this year [1]. Critical functions of breathing, swallowing and speech may be decimated by the disease if not by our treatments for the disease. Thus, modern head and neck cancer care strives to achieve a delicate balance between maximizing survival, functional outcomes and quality of life.

Classically, advanced laryngeal cancer was treated with primary total laryngectomy (TL) and post-operative radiation therapy (PORT); the sole focus was survival. After the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group Trial [2] and RTOG 91-11 trials [3], the treatment paradigm shifted towards organ preservation strategies and chemo-radiation therapy (CRT) became the standard of care [4,5]. For over two decades, most North American cancer treatment centers applied CRT widely to advanced laryngeal cancers assuming it would provide the optimal outcomes. However, in 2006 data from the National Cancer Data Base (NCDB) demonstrated that laryngeal cancer was the only cancer in the United States with a declining survival rate [4]. This observation coincided with the increased use of RT/CRT, and decreased application of TL since the publication of the VA trial in 1991 [4–6]. In 2005 population-based analyses of survival began entering the literature with multiple demonstrations that the widespread application of RT/CRT to advanced laryngeal cancers did not necessarily reflect the outcomes of landmark trials [7–10,11,12]. Many patients treated with CRT today have lesions that would not have met criteria for inclusion in the landmark trials because they are too extensive. Moreover, the data has also shown that not all advanced laryngeal cancers are created equal [13].

Despite the landmark trials basing treatment decisions on overall cancer stage [14], the majority of treatment algorithms are based on T-

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classification [15]. Much data has emerged showing that T3 and T4 laryngeals cancer have distinct responses to RT/CRT [10,11,16]. While it has generally become accepted that T4a cancers respond better to laryngectomy [12,15,17], there are a wide range of outcomes for T3 cancers [7,9–11,18–21]. T3 laryngeal cancers can be categorized by N stage, subsite, pre-treatment laryngeal/pharyngeal function, patient health status, patient preference as well as tumor volume [22]. While most T3 laryngeal cancers will have improved long-term survival with TL and RT/CRT, there are subsets of glottic cancer patients, which seem to have excellent long-term survival and function with organ preservation [16,22]. In 1997 it was found that glottic cancers with a tumor volume of ≤3.5 cc on pre-treatment computed tomography (CT) scans had excellent locoregional control rates [22]. Thus, at the University of Florida, it has been the strategy of the multidisciplinary head and neck tumor board to include tumor volume during treatment making decisions.

This study was designed to assess survival outcomes of T3 glottic cancers treated at the University of Florida based on a strategy, which incorporates tumor volume into head and neck tumor board treatment recommendations. The objectives were to: (1) compare survival outcomes of patients treated with organ preservation by tumor volume (2) determine if tumor volume continues to be a significant prognostic predictor for T3 glottic cancer survival.

## Materials and methods

Institutional review board research ethics approval was granted at the University of Florida in accordance with the Health Insurance Portability and Accountability Act. This study was performed at a tertiary care academic referral center.

### *Setting and study design*

Data were collected from inpatient and outpatient records of the Head and Neck Oncology Team at the University of Florida Health/Shands Hospital system. The design was a retrospective cohort study with data collected from June 1966 to July 2016.

### *Patient selection*

Review of a prospectively collected outcomes tracking database was performed. All cases of laryngeal cancer were reviewed. Inclusion criteria were defined as: age ≥18 years, biopsy proven squamous cell carcinoma (SCC) of the glottic larynx, clinically T3 tumor with at least a paralyzed true vocal cord +/− minor cartilage invasion, and curative intent treatment at the University of Florida with primary organ preservation

Exclusion criteria were defined as: palliative treatment, non-compliance with prescribed treatment, second primary tumor, previous head and neck cancer with or without treatment, any part of treatment received at an outside institution or distant metastases at the time of diagnosis. Patients with mobile vocal cords were excluded because they have a more favorable outcome. This study focuses on patient with vocal cord fixation as those patients tend to have a worse survival rate [23].

### *Data collection*

All patients diagnosed with glottic laryngeal cancer who received organ preservation treatment at the University of Florida were identified in a prospective database. Inclusion criteria were then applied to obtain an initial population. The database was used to extract relevant demographic, tumor, treatment, follow-up and survival data. A secondary review was conducted using physical and electronic outpatient and inpatient charts to confirm data accuracy and completeness. Exclusion criteria were then applied to obtain a final population for

**Table 1**
Patient and tumor variables by treatment group.

| Variable | Group | | p-Value |
|---|---|---|---|
| | RT | CRT | |
| N (%) | 85 (79) | 22 (21) | |
| Age | | | |
| < 60, no. (%) | 34 (40) | 10 (45) | 0.64 |
| > 60, no. (%) | 51 (60) | 12 (55) | |
| Median [range], yrs | 61 [29–83] | 61 [35–89] | 0.76 |
| Gender, no. (%) | | | |
| Male | 79 (93) | 19 (86) | 0.39 |
| Female | 6 (7) | 3 (14) | |
| Race | | | |
| African American | 10 (12) | 0 (0) | 0.12 |
| Other | 75 (88) | 22 (100) | |
| CCI | | | |
| 0–3 | 29 (34) | 9 (41) | 0.24 |
| 4–6 | 45 (53) | 9 (41) | |
| ≥7 | 6 (7) | 4 (18) | |
| Unknown | 5 (6) | 0 (0) | |
| ECOG | | | |
| 0 | 75 (89) | 17 (77) | 0.13 |
| 1 | 6 (7) | 1 (5) | |
| 2 | 2 (2) | 1 (5) | |
| 4 | 2 (2) | 3 (14) | |
| Smoking | | | |
| Median [range], pyh | 50 [20–138] | 48 [2–200] | 0.30 |
| Smoking after treatment | | | |
| No | 26 (31) | 13 (59) | 0.18 |
| Yes | 27 (32) | 6 (27) | |
| Unknown | 32 (37) | 3 (14) | |
| cN-classification, no. (%) | | | |
| N0 | 68 (80) | 18 (82) | 1.0 |
| N1 | 11 (13) | 2 (9) | |
| N2a | 0 (0) | 0 (0) | |
| N2b | 5 (6) | 1 (5) | |
| N2c | 0 (0) | 1 (5) | |
| N3 | 1 (1) | 0 (0) | |
| Overall stage, no. (%) | | | |
| III | 79 (93) | 19 (86) | 0.66 |
| IV | 6 (7) | 2 (9) | |

Abbreviations: CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Group performance status; RT, external beam radiation therapy; CRT, chemotherapy and external beam radiation therapy, no., number; yrs, years; cN, clinical N-classification.

**Table 2**
Distribution of tumor volumes between treatment groups.

| Variable | Group | | 2 year local control (%) | 5 year local control (%) |
|---|---|---|---|---|
| | RT | CRT | | |
| Number with tumor volume data | 40 | 20 | | |
| Tumor volume (cc), no. (%) | | | | |
| ≤1.0 | 4 | 0 | 92% | 81% |
| ≤1.5 | 14 | 0 | | |
| ≤2.0 | 17 | 2 | | |
| ≤2.5 | 22 | 4 | | |
| ≤3.0 | 28 | 4 | 65% | 57% |
| ≤3.5 | 32 | 6 | | |
| ≤4.0 | 34 | 8 | | |
| ≤4.5 | 36 | 10 | 50% | 43% |
| Median, cc | 2.4 | 4.6 | | |
| Range, cc | 0.4–7.7 | 1.6–9.2 | | |

Abbreviations: RT, external beam radiation therapy; CRT, chemotherapy and external beam radiation therapy; no., number; cc, cubic centimeters.