

Quality of Life for Patients Following Total Laryngectomy vs Chemoradiation for Laryngeal Preservation

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Background: The incorporation of chemotherapy and radiation, either sequentially or concurrently, has been increasingly used for organ preservation in patients with advanced laryngeal cancer. Traditional outcome measures of clinical response such as locoregional control and survival have been similar for patients treated with chemoradiotherapy and those treated with total laryngectomy (TL). The impact of concurrent chemoradiotherapy for laryngeal preservation on the overall quality of life (QOL) of patients has not been clearly evaluated, particularly in direct comparison with TL.

Objective: To compare the QOL of patients treated with concurrent chemoradiotherapy with those treated with TL.

Design: Nonrandomized, retrospective, cross-sectional study.

Setting: Academic tertiary care referral center.

Methods: The study included 42 patients with advanced stage III or IV cancer of the larynx, who were treated with either concurrent chemoradiotherapy or TL with postoperative radiation therapy. Patients had to be without evidence of recurrence and to have completed therapy at least 3 months prior to inclusion in the study.

Quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) in tandem with the head and neck module (EORTC QLQ-H&N35).

Results: On the core questionnaire (QLQ-C30), there were no statistically significant differences in the overall QOL score between the 2 groups. Functional subscale analysis revealed a trend for patients in the surgery and radiotherapy group to experience greater difficulties with social functioning ($P=.18$) relative to the chemoradiation group. On the QLQ-H&N35, surgery patients reported significantly greater difficulties with sensory disturbances (smell and taste, $P=.001$), use of painkillers ($P=.049$), and coughing ($P=.004$). On the other hand, chemoradiation patients reported significantly greater problems with dry mouth ($P=.02$).

Conclusions: Both chemoradiation and TL affect, albeit differently, the QOL of patients treated for advanced cancer of the larynx. Although these differences can be detected by functional and subscale analysis, the overall QOL scores of both groups seem similar.

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SURGICAL RESECTION OF advanced cancer of the larynx commonly involves total laryngectomy (TL), which results in significant anatomic and functional alterations such as a permanent tracheostoma and loss of laryngeal speech. As an alternative to surgical resection, laryngeal preservation may be achieved in patients with advanced cancer of the larynx by chemotherapy and radiation, administered either sequentially or concurrently, or by radiation therapy only. In 1991, the Radiation Therapy Oncology Group (RTOG) initiated a 3-arm randomized prospective study (RTOG 91-11) to compare the efficacy of induction chemotherapy followed by radiation, concurrent

chemoradiotherapy, and radiation therapy only in preserving the larynx in patients with advanced laryngeal cancer.¹ The preliminary analysis of this trial found that the highest rate of organ preservation was in patients treated with concomitant radiation and chemotherapy; however, no significant difference in survival was obtained among the 3 arms. With comparable survival rates among these treatment options, the relative impact of each treatment on patients' quality of life (QOL) becomes critical in selecting the "optimal" therapeutic approach.

A number of studies have examined functional and behavioral outcomes for patients with laryngeal cancer treated with either surgery or chemotherapy and radia-

Table 1. Demographic Characteristics of Treatment Groups

Characteristic	Laryngectomy and Radiotherapy	Chemoradiation
Age, mean (SD), y	65.6 (10.3)	60.8 (8.6)
Sex, No. (%)		
Male	20 (87)	13 (68)
Female	3 (13)	6 (32)
Marital status, No. (%)		
Single	1 (4)	3 (16)
Married	14 (61)	10 (53)
Separated/divorced	7 (30)	5 (26)
Widowed	1 (4)	1 (5)
Ethnicity, No. (%)		
African American	5 (22)	2 (10)
White	18 (78)	17 (90)

tion, but none of these studies simultaneously compared the outcomes of these treatments.²⁻⁴ Other studies have compared QOL outcomes of patients treated with laryngectomy with those treated with radiotherapy alone,^{3,5} or to those treated with sequential neoadjuvant chemotherapy followed by radiation.⁶ Unfortunately, very little information is available concerning the differences in QOL outcomes among patients treated with either concurrent chemoradiation or surgery and adjuvant radiation. Although concurrent chemoradiotherapy has higher rates of organ preservation compared with chemotherapy followed by radiation or radiation therapy alone, it is also associated with a higher rate of toxic effects and treatment-related complications.⁷ Both increased efficacy and higher rate of toxic effects are attributed to the radiosensitizing effects of chemotherapy. The impact of this increased morbidity on patients' QOL needs to be carefully assessed. Therefore, the aim of our study was to assess QOL in patients with advanced laryngeal/hypopharyngeal cancers that were treated with concurrent chemoradiotherapy and compare it with those treated with TL.

METHODS

PATIENTS

Patients with stage III or IV laryngeal cancer, who were treated with either TL or concurrent chemoradiation for laryngeal preservation, were included in this study. Patients had to have completed treatment at least 3 months prior to inclusion in the study. This was done to allow for the short-term effects of treatment to subside prior to QOL assessment. Information concerning medical and demographic variables was abstracted from medical records. Of 152 consecutive patients identified by the Arkansas Cancer Research Center Tumor Registry for possible inclusion in the study, 80 were still alive at the time of data collection. Fifty-four patients completed QOL questionnaires (68% questionnaire response rate): 44 patients completed the assessments during routine clinic visits, and 10 patients completed surveys via mail. Twelve packets were eliminated from the analyses owing to missing data, leaving a final sample of 42.

Twenty-three participants were treated with surgery and radiation, and 19 patients were treated with concurrent chemoradiation therapy. Surgical treatment included TL with neck dissection and postoperative radiation therapy. Patients treated with chemoradiotherapy for laryngeal preservation received standard fractionation (1 fraction per day, 180-200 rad [1.8-2.0 Gy] per

fraction, 5 days per week, and total dose of 6600-7200 rad [66-72 Gy] radiation therapy. All patients in this group received at least 2 cycles of cis-platinum and fluorouracil, concurrently with radiation therapy. Patients with less than a complete response to chemoradiotherapy (n=4) underwent salvage surgery. Mean follow-up was 36 months.

QOL MEASURES

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ) were used to assess QOL outcomes. The core questionnaire (QLQ-C30) is a widely used, multidimensional measure of health-related QOL for cancer patients. It includes 30 items comprising 6 functional scales (ie, physical, role, cognitive, emotional, and social functioning, and global QOL), 3 symptom scales (ie, fatigue, pain, and emesis), and 6 individual items (dyspnea, sleep disturbance, appetite, constipation, diarrhea, and financial impact). The core instrument was used in conjunction with the head and neck module (QLQ-H&N35), a 35-item measure intended to assess symptoms specific to head and neck cancer. The QLQ-H&N35 yields 7 multiple-item scales (pain, swallowing, senses, speech, social eating, social contact, and sexuality), and 10 single items relating to problems with teeth, dry mouth, cough, opening the mouth wide, sticky saliva, weight loss, weight gain, use of nutritional supplements, feeding tubes, and painkillers. The core instrument has been validated in multiple studies with patients with cancer, including those with head and neck disease.⁸⁻¹¹ The more recently developed QLQ-H&N35 has also demonstrated good psychometric properties in studies of patients with head and neck cancer in Europe^{10,12} and the United States.¹³ All EORTC scales were scored and linearly transformed to 0- to 100-point scales. The functional scales were reverse scored, so that higher scores represent better functioning. Higher scores on the symptom and individual item scales indicate greater difficulties.

Data were analyzed using NCSS 7.0.22 statistical analysis software (NCSS Statistical Software, Kaysville, Utah). Non-parametric χ^2 and Wilcoxon rank sum analyses were used to assess group differences on demographic and medical variables. Wilcoxon analyses were used to test for differences between the surgery and chemoradiotherapy groups on the EORTC scales. Tests were 2-tailed, and $P<.05$ was considered significant. In view of the exploratory nature of the study, $P<.20$ was reported as a trend.

RESULTS

The first analysis compared patients with successful laryngeal preservation (n=15) with those who underwent TL (n=27). In this analysis, patients initially treated with chemoradiation who subsequently received salvage laryngectomy were included in the surgery group. The 2 groups did not differ significantly with respect to age, sex, marital status, or ethnicity (**Table 1**). Descriptive statistics for the EORTC questionnaires are presented in **Table 2**. The average time of QOL evaluation was 15 months from completion of treatment (range, 3-53 months) and was not significantly different between both groups.

On the core questionnaire (QLQ-C30), there was a trend for patients in the surgery and radiotherapy groups to experience greater difficulties with social functioning ($P=.18$) relative to the chemoradiation group. Though not statistically significant, the group difference in medians on this scale was 33 points. On the QLQ-H&N35, surgery patients reported significantly greater difficul-

Table 2. EORTC QLQ-C30 and QLQ-H&N35 Descriptive Statistics for Laryngectomy and Radiotherapy and Chemoradiation Therapy Groups*

	Laryngectomy and Radiotherapy		Chemoradiation		
Scale	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	P Value
EORTC QLQ-C30					
Physical functioning	60.0 (0-100)	69.6 (29.0)	100.0 (20-100)	78.7 (27.7)	NS
Role functioning	66.6 (0-100)	70.3 (29.7)	66.6 (0-100)	72.2 (29.3)	NS
Social functioning	66.6 (17-100)	61.7 (31.3)	100.0 (0-100)	74.4 (33.8)	.18
Emotional functioning	66.4 (0-100)	66.4 (30.4)	66.4 (8-100)	73.0 (27.0)	NS
Cognitive functioning	83.3 (33-100)	79.0 (22.4)	83.3 (33-100)	84.4 (20.4)	NS
Quality of life	66.4 (25-100)	65.8 (23.1)	58.1 (17-100)	63.6 (27.5)	NS
Fatigue	33.3 (0-100)	35.8 (26.2)	44.4 (0-78)	30.4 (28.3)	NS
Pain	16.7 (0-100)	23.4 (27.0)	16.7 (0-83)	26.6 (28.0)	NS
Nausea/vomiting	0.0 (0-50)	9.9 (14.8)	0.0 (0-50)	6.7 (15.2)	NS
EORTC QLQ-H&N35					
Pain	0.0 (0-83)	14.4 (22.0)	8.3 (0-91)	22.7 (28.8)	NS
Swallowing	16.6 (0-100)	26.4 (30.8)	16.6 (0-75)	31.5 (31.7)	NS
Senses	66.6 (0-100)	59.2 (34.4)	16.7 (0-83)	20.0 (28.3)	.001
Speech	33.3 (0-78)	29.7 (23.6)	11.1 (0-67)	22.2 (26.6)	NS
Social eating	16.6 (0-100)	30.1 (33.5)	8.3 (0-100)	25.5 (31.6)	NS
Social contact	6.7 (0-93)	15.0 (20.4)	6.7 (0-40)	12.4 (15.7)	NS
Sexuality	0.0 (0-100)	22.8 (27.8)	16.6 (0-100)	36.7 (43.7)	NS
Teeth	0.0 (0-100)	22.2 (33.3)	0.0 (0-67)	11.1 (20.6)	NS
Open mouth	0.0 (0-100)	16.0 (31.2)	0.0 (0-100)	22.2 (32.5)	NS
Dry mouth	0.0 (0-67)	18.5 (26.7)	33.3 (0-100)	37.8 (27.8)	.02
Sticky saliva	0.0 (0-100)	29.6 (35.0)	33.3 (0-100)	40.1 (31.4)	NS
Coughed	66.7 (0-100)	69.2 (35.2)	33.3 (0-67)	37.8 (24.8)	.004
Felt ill	33.3 (0-100)	27.2 (32.1)	33.3 (0-67)	20.0 (21.1)	NS
Painkillers	100 (0-100)	59.3 (50.1)	0.0 (0-100)	26.7 (45.8)	.049
Nutritional supplements	0.0 (0-100)	37.0 (49.2)	0.0 (0-100)	40.0 (50.7)	NS
Feeding tube	0.0 (0-100)	22.2 (42.4)	0.0 (0-100)	26.7 (45.8)	NS
Weight loss	0.0 (0-100)	18.5 (39.6)	0.0 (0-100)	20.0 (41.4)	NS
Weight gain	0.0 (0-100)	40.7 (50.1)	0.0 (0-100)	20.0 (41.4)	NS

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EORTC QLQ-H&N35, head and neck module of EORTC QLQ-C30; NS, nonsignificant ($P \geq .05$).

*Higher scores on the functioning scales (physical, role, social, emotional, cognitive, quality of life) indicate better functioning. Higher scores on all remaining scales indicate greater impairment.

ties with sensory disturbances (smell and taste, $P = .001$), use of painkillers ($P = .049$), and coughing ($P = .004$). On the other hand, chemoradiation patients reported significantly greater problems with dry mouth ($P = .02$).

The analyses were then repeated using intent-to-treat principles; patients who were initially treated with chemoradiation therapy and subsequently received salvage laryngectomy ($n = 4$) were retained in the chemoradiation group. This was done to determine whether patients initially treated with chemoradiation therapy (regardless of whether they subsequently received salvage laryngectomy) differed from patients who received laryngectomy and radiation as their primary treatment. This analysis provides information about QOL outcomes according to the type of treatment that was initially planned and administered as opposed to the treatment that was ultimately received. Results were similar to the prior analyses but less pronounced. There were no significant group differences on the core questionnaire. On the QLQ-H&N35, surgery patients reported significantly greater difficulties with sensory disturbances ($P = .001$). They also demonstrated a trend toward greater problems with coughing ($P = .13$); the difference in group medians for this scale was 33 points. Conversely, chemoradiation patients reported signifi-

cantly greater problems with dry mouth ($P = .009$), with a trend toward more sexual concerns ($P = .08$, median difference of 33 points).

COMMENT

Until recently, many QOL studies in head and neck cancer focused exclusively on deficits in physical functioning (eg, speech, swallowing, and eating).¹⁴⁻¹⁷ In the last few years, a number of better-validated, more comprehensive health-related QOL instruments have become available to assess the impact of illness on the overall QOL of patients.

Health-related QOL instruments can be divided into general and disease-specific instruments. General measures assess the overall impact of patients' health status on their QOL and cover a broad spectrum of functional, physical, psychological, and social domains. Their main advantages are that they can be used across a broad range of patients and allow comparison of results across different diseases. Examples of general measures include the Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey (SF-36),¹⁸ and the Sickness Impact Profile.¹⁹ The disadvantage of general instruments is their lack of responsiveness to the peculiar aspects of a certain disease process. Disease-specific instruments allow

comparisons of QOL outcomes of patients with a similar disease process (eg, cancer). Examples of cancer-specific QOL instruments include the Functional Assessment of Cancer Therapy (FACT) scale²⁰ and the Functional Living Index–Cancer (FLIC).²¹ These instruments are often more responsive to patients with cancer and to the change in their health status over time than general measures.

Site-specific cancer instruments are designed to be most sensitive to the functional deficits peculiar to the affected organ system. The head and neck region provides a very dramatic example of this concept. Disturbances of voice, speech, breathing, mastication, deglutition, sense of taste and smell, and facial appearance are but a few examples of such deficits that are peculiar to patients with cancer of the head and neck.²² Examples of head and neck-specific instruments include the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN),²³ the University of Washington Head and Neck Questionnaire (UW QOL),²⁴ and the University of Michigan Head and Neck Quality of Life questionnaire.²⁵ Treatment-specific instruments have also been developed to capture the impact of specific treatment-related complications on QOL; for example, the Head and Neck Radiation Therapy Questionnaire (HNRQ) contains items detailing the assessment of mucositis, skin reactions, xerostomia, nausea, vomiting, appetite, and energy level.²⁶

To obtain a broad yet relevant assessment of QOL in cancer patients, investigators have increasingly employed a “modular” approach, in which a general QOL instrument is combined with a site- or treatment-specific measure.²² The present study used such a modular approach by using the EORTC core instrument (QLQ-C30), a widely used, multidimensional measure of health-related QOL for cancer patients, combined with a head and neck-specific module (QLQ-H&N35). The core instrument has been validated in multiple studies with cancer patients, including those with head and neck disease.⁸⁻¹¹ The more recently developed QLQ-H&N35 has also demonstrated good reliability, validity, and responsiveness in studies of patients with cancer of the head and neck in Europe¹² and the United States.¹³ The use of both instruments in a modular fashion has been recently validated in a 12-country field study of patients with cancer of the head and neck.²⁷ In a recent study of 120 patients with head and neck cancer, we have found that the head and neck module (QLQ-H&N35) of the questionnaire provided unique information that was not measurable with the core instrument (QLQ-C30), supporting the rationale for using this modular approach in patients with cancer of the head and neck.¹³

In the present study, we found few differences in QOL outcomes among patients treated with either TL or concurrent chemoradiation. Patients treated with chemoradiation therapy reported greater difficulties with dry mouth. In contrast, patients treated with laryngectomy reported greater problems with taste and smell, greater reliance on pain medications, more difficulties with coughing, and trends toward poorer social functioning, compared with those successfully treated with chemoradiation. The results concerning increased use of painkillers among laryngectomy patients are consistent with those of the Veterans Affairs (VA) Laryngeal Cancer Study Group in which laryngectomy patients

reported significantly higher pain scores.⁶ While the present study did not find differences in self-reported pain severity, the elevated use of pain medication among laryngectomy patients suggests that pain may be a more prominent concern for these patients relative to those successfully treated with organ preservation. Additionally, both the present study and the VA Laryngeal Cancer Study Group⁶ found trends toward more disrupted social functioning among laryngectomy patients compared with those who had successful laryngeal preservation. Disfigurement, disrupted body image, social anxiety, or impaired communication as a result of surgery may each play a role in eroding the quality of important relationships and social functioning. In a study of head and neck cancer patients successfully treated with surgery, Gamba and colleagues²⁸ reported poorer self-image, increased social isolation, and greater deterioration in intimate relationships and sexuality among those with the most extensive disfigurement.

While there were few differences in subscale analysis, the results of the present study found no significant differences in the overall QOL scores (ie, either global QOL scores or module total scores) between patients treated with TL and those treated with concurrent chemoradiotherapy. This is similar to the findings from the VA Laryngeal Cancer Study, in which sequential rather than concurrent chemoradiotherapy was used for laryngeal preservation.⁶ This is somewhat surprising, since one would have expected that preservation of the larynx would have been associated with less functional deficits and better QOL. Additionally, the absence of group differences in this study concerning speech and swallowing is also surprising. Based on our clinical observations, we had anticipated greater impairment of speech among laryngectomy patients and greater swallowing difficulties in patients who underwent chemoradiation. Using different QOL instruments, Terrell et al⁶ similarly found no significant group differences in speech or eating problems in their sample of long-term survivors of the VA Laryngeal Cancer Study. The lack of significant differences in these functional domains or overall QOL scores between the 2 groups may be explained by several factors.

First, the lack of significant difference in speech scores between patients treated with laryngectomy or laryngeal preservation in the present study may be explained by the liberal use of primary voice restoration using tracheoesophageal prosthesis at the time of laryngectomy, followed by an intensive program of voice and speech rehabilitation. This may have buffered perceived speech problems among laryngectomy patients. Second, since radiation therapy was used in both groups of patients in the present study, differences in radiation-related long-term complications, such as dysphagia, may have been obscured. Third, this cross-sectional study intentionally evaluated patients at least 3 months after treatment, and most patients (75%) had completed their therapy, for at least a year. The average time of evaluation for the whole group was 15 months (3-53 months) after completion of therapy, and was not significantly different among both groups. This time interval allowed patients' recovery from the short-term effects of treatment, whether surgery or chemoradiotherapy. We and others have demonstrated that QOL scores of patients with

cancer of the head and neck deteriorated significantly during treatment, followed by a slow recovery until the 12-month follow-up.^{13,29} It is possible that differences in QOL scores between both groups during the acute phase of treatment were neutralized by this recovery period.

Finally, and perhaps most importantly, the ability of surviving patients to cope with the functional deficits resulting from treatment should not be underestimated. We recently studied coping strategies among 120 patients with cancer of the head and neck during different phases of treatment and found that these strategies greatly impact patients' perceptions of their QOL.³⁰ The physical deficits that are considered as significant by clinicians are often different from the QOL dimensions that are emphasized by patients themselves.³¹⁻³³ More attention and future research should be directed toward the emotional, social, and family challenges that patients may experience in the aftermath of aggressive treatment for advanced disease.

There are several limitations to our study. The analysis is retrospective in nature and compares 2 nonrandomized groups of patients. Factors influencing the choice of treatment were not controlled. The decision to choose TL vs laryngeal preservation was based primarily on patients' preferences. This a priori preference may have an impact on subsequent QOL analysis. Similarly the treatments in each group, although are somewhat uniform, were not standardized. For example, patients treated with TL may have had a unilateral or bilateral, radical or modified radical or selective neck dissection, depending on the site and stage of disease. All patients treated with organ preservation received at least 2 courses of chemotherapy during radiation, but some patients received 3 or 4 courses. These differences in treatment may also affect QOL scores and limits the generalized applicability of the results.

Another limitation is the cross-sectional nature of the analysis. Although all patients were evaluated at least 3 months after treatment and most (75%) at least 1 year after (average, 15 months), the differences in timing of the analysis may have affected QOL scores. These limitations should be considered in designing future prospective clinical trials evaluating the impact of treatment on QOL of patients with advanced cancer of the larynx.

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