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EDITORIAL

T4 Laryngeal Cancer With Good Function: Should We Be Reluctant to Treat Without Surgery?

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Despite scientific training, oncologists are subject to confirmation bias, which is the tendency to interpret new evidence as confirmation of one's existing beliefs or theories.

That surgery cures many solid tumors is obvious. Experience has shown that the recurrence risk for some cancers is reduced with the administration of adjuvant postoperative radiation treatment. Some solid tumors are cured through treatment with radiation as the primary modality. Which cancers are best addressed through resection and which through radiation treatment? Oncologists' opinions are informed by their experience and expectations but can also be affected by a desire to support preconceptions. What should we do? Randomized trials are difficult to perform, especially when investigators lack equipoise colored by their existing beliefs.

In addition, financial incentives and legitimate desires to do "what is best" for the patient can impede progress. It has been said that in the United States, only the Veterans Administration could have completed a trial of laryngectomy versus radiation for advanced laryngeal cancer (1). Nonetheless, current nonoperative management of advanced laryngeal cancer is firmly based on the results from prospective, randomized trials. We have moved from total laryngectomy with adjuvant radiation through to induction chemotherapy followed by radiation (2), to

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concurrent chemoradiation (3). It is not surprising that the rate of nonoperative management of advanced squamous cell carcinomas of the larynx has increased (4-7). This has excited some concern. Hoffman et al (8) described the decreasing survival of American laryngeal cancer patients from 1974 to 1999, prompting some to ascribe the decline to popularization of nonoperative treatment (9).

Recently, the American Society of Clinical Oncology (ASCO) published a Clinical Practice Guideline Update addressing larynx-preservation strategies in the treatment of laryngeal cancer (10). In the abstract, the recommendations state, "For patients with locally advanced (T3, T4) disease, organ-preservation surgery, combined chemotherapy and radiation or radiation alone offer the potential for larynx preservation without compromising overall survival." Clear, and supported by prospective, randomized data.

Significantly, the new recommendation 2.2 observes that, "For selected patients with extensive T3 or large T4a lesions and/or poor pretreatment laryngeal function, better survival rates and quality of life may be achieved with total laryngectomy rather than with organ-preservation approaches and may be the preferred approach." However, the statement regarding extensive T3 or large T4a conflicts with the statement given in the abstract.

Recommendation 4.1 states "… patients with a nonfunctional larynx (eg, extensive T3 or T4a) or tumor penetration through cartilage into surrounding soft tissues are considered poor candidates for a larynx-preservation approach. Primary surgery, usually total laryngectomy, is commonly recommended in this setting."

We agree that patients with poor function who are unlikely to regain or maintain safe swallowing are poor candidates for laryngeal preservation. Potentially dangerous episodes of aspiration are always a major source of concern. However, it might be incorrect to equate poor larynx function with extensive T3 or T4a disease. Some patients with paralyzed vocal cords, some with T3 or T4a disease, and some with "bulky" tumors can safely swallow solids and liquids and have a serviceable voice. Whether radiation treatment as the primary modality can cure such a lesion while preserving laryngeal function remains subject to debate; however, most head and neck oncologists believe that a functional larynx is preferable to a postlaryngectomy state, even with modern voice restoration.

Some statements within the ASCO guidelines discourage attempts at laryngeal preservation that might be in the best interests of our patients. Many of the studies examining the survival of patients with T4 laryngeal cancer have been flawed. More recent reports have attempted to adjust for recognized sources of bias and are more valuable. The arguments regard T4a disease, because most viable patients with T4b disease are necessarily treated with a nonoperative approach. However, databases poorly distinguish T4a from T4b disease.

Selection bias is a nearly unsurmountable problem when using historical databases. Patients with better insurance and supportive families are considered better candidates for surgery, leaving isolated, poorer patients to receive nonoperative treatment, which they are less likely to complete (6). The presence of comorbidities has not been rigorously documented in nonoperative patients. In the United States, it is in the hospital's financial interest to record comorbidities. However, radiation oncologists and medical oncologists, who are almost always treating on an outpatient basis, have little incentive to document even major comorbidities.

Outcomes are better at "centers of excellence." Surgery involves a preoperative evaluation, followed by an intense surgical and perioperative experience, but the episode of care is short. Because the duration for delivery of radiation and chemotherapy spans weeks, nonoperative patients are more likely to be treated with curative intent locally rather than traveling to a high-volume center. Treatment at a teaching and/or research center was significantly associated with laryngectomy rather than chemoradiation therapy, suggesting that patients will seek surgical expertise but are less likely to pursue experienced nonoperative teams (11).

Some of the T4 patients relegated to nonoperative management will not be able to tolerate concurrent systemic therapy. The Dutch Head and Neck Society recommended total laryngectomy with adjuvant radiation for patients with T4 disease. However, if ill and unresectable T4 laryngeal cancer patients are the only ones to receive nonoperative treatment, the presence of a selection bias is ensured. A longitudinal study showed that the incidence of T4 patients treated with radiation alone increased and the total laryngectomy rate decreased, but the incidence of combined chemotherapy and radiation was relatively stable, consistent with the premise that more patients were being treated with curative intent but that many could not tolerate systemic therapy (4).

Chen et al have produced several monographs on this subject, and the ASCO review (10) referenced their 2007 report (12). Their more recent work, reported by Lin et al (6) used a Surveillance, Epidemiology, End Results−Medicare-linked data set and included patients with American Joint Committee on Cancer, sixth edition, stage III or IVa cancer with nodal disease. Those with localized disease were excluded. Patients with chemotherapy and radiation claims within 90 days were considered to have received concurrent chemoradiation. To the best of our knowledge, this is the only study to assess whether patients completed their radiation and chemotherapy regimens. At 5 years, the overall survival for these stage III and IVa patients who had undergone initial surgery was 37.6% compared with 37.1% for the patients completing chemoradiation ($P = .78$, log-rank test). Chen's more recent data (6) deserve more attention.

We wholeheartedly endorse the belief that patients with little prospect of regaining laryngeal function (whether because of a lack of support, compliance issues, or extensive destruction of the laryngeal framework) and those who are persistent smokers (13, 14) are poor candidates for

laryngeal preservation. For such patients, laryngectomy is preferred.

However, head and neck oncologists lack recent prospective, randomized survival data for patients with resectable, functional, T4 laryngeal cancer. In the Veterans Administration trial, although patients with T4N0 laryngeal cancer (n = 41) had improved survival with surgery followed by adjuvant radiation, the entire T4 cohort (n = 84) had no significant differences in survival (15). This might be attributable to a benefit from systemic therapy for T4N+ patients. Modern imaging might reclassify many of the T3 patients in the Veterans Administration study to T4, warranting investigation. The decreased survival for T4Nany patients found in retrospective studies might be a reflection of radiation oncologists enlarging the pool of patients offered curative nonoperative therapy; however, that decrease is narrowing (7).

Although systemic therapies have not advanced in decades, staging, radiation, and surgical results have improved. The ASCO guidelines note, "…overall survival of patients with stage III/IV laryngeal cancer diagnosed from 1992 to 2009, irrespective of treatment, has significantly improved over time" (10) (Figs. 1 and 2). Closer perusal of the analysis of advanced laryngeal cancer by Megwalu and Sikora (7) shows that despite the selection bias, geographic obstacles pushing more surgical patients to high-volume centers, differences in recording comorbidities, and the use of nonoperative strategies for patients who could not complete concurrent chemoradiation as prescribed, with time, the nonoperative results have been becoming better, not worse, for both disease-specific and overall survival for patients with advanced laryngeal cancer. The gaps between nonoperative and surgical outcomes have narrowed, despite the performance of fewer laryngectomies.

After a long period of stagnation, systemic therapy seems be improving. Although validated biomarkers that predict the outcome of nonoperative treatment have not been defined (10), the tumor volume, pattern of growth, molecular profile, or some other tumor-related factor could prove important. A completed randomized trial of laryngectomy with appropriate adjuvant therapy versus optimal nonoperative treatment of resectable T4 larynx cancer patients with good function would be integral to the progressive improvement in our care of these patients. However, completing such a large, randomized trial in the United States would be challenging. The incidence of T4 laryngeal cancer and other substance use-related cancers is decreasing in North America and elsewhere (4, 5), and patients are typically reluctant to participate in a randomized trial comparing surgical and nonsurgical management. The current frenzy surrounding new agents also limits enthusiasm for embarking on a trial that will take years to complete.

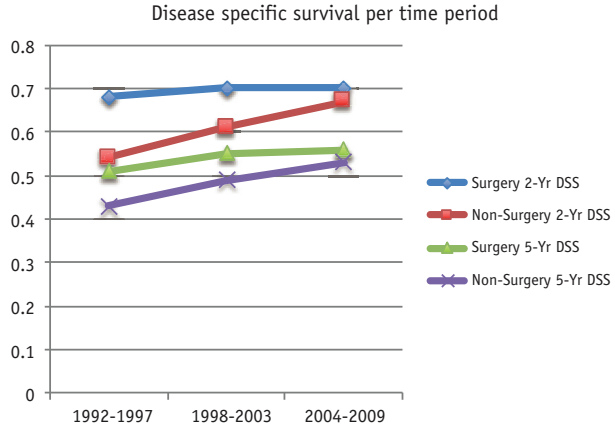

Fig. 1. Graph showing differences in disease-specific survival (DSS) over time. Data from Megwalu and Sikora (7).

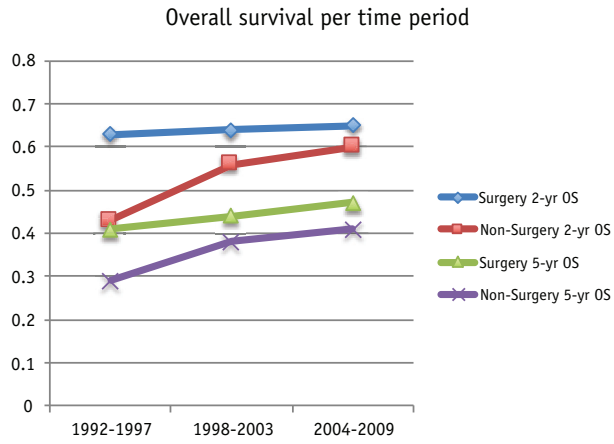

Fig. 2. Graph showing differences in overall survival (OS) over time. Data from Megwalu and Sikora (7).

For patients who receive larynx-conserving therapy, most head and neck oncologists have continued to deliver care to patients with T4 lesions based on a regimen tested on predominantly T3 disease and designed 30 years earlier (16). Although more T4 patients are receiving treatment with curative intent, the results with nonoperative therapy have improved.

The therapeutic community should conduct randomized phase II studies designed to improve on that standard of care. Improved radiosensitization might not be the best use of systemic agents and the profession should embrace other approaches. Appreciating that some patients will be best served by "upfront" total laryngectomy, such studies should carefully define the eligibility for nonoperative management in terms of laryngeal function and tumor characteristics. We can, and should, aspire to do better for our patients.

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