EDITORIAL

REEXAMINING THE TREATMENT OF ADVANCED LARYNGEAL CANCER

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Determining the standard of care for a cancer with a diverse set of treatment variables is difficult. Advanced laryngeal cancer is one such case. The treatment for advanced laryngeal cancer is now at a point where the current standard of care—concurrent chemotherapy and radiotherapy with surgical salvage (ie, laryngectomy)—must be reexamined. Why? Because published studies—identified as evidence-based medicine—have set a standard of care that has resulted in major unintended consequences.

The survival of patients with laryngeal cancer should not be decreasing. Unfortunately, this is happening today. The focal points of this commentary are (1) how these unintended consequences leading to decreased survival have occurred, (2) what can be done to avoid similar outcomes in the future, and (3) how the current standard of care for laryngeal cancer should be changed.

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STUDIES LEADING TO THE CURRENT STANDARD OF CARE

Studies that are used to determine standard of care must be accurate and reproducible, must have no major unintended consequences of the treatment studied, and must make no unwarranted conclusions. Two clinical studies have had major effects on the management of advanced laryngeal cancer in the United States. The first, in 1991, was the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group.[1] This study of select patients found that induction chemotherapy and radiotherapy resulted in little difference in survival compared with that in patients receiving total laryngectomy and postoperative radiotherapy.[1] The second study, the Radiation Therapy Oncology Group (RTOG) 91-11 study, published in 2003, reported that concurrent chemotherapy and radiotherapy (RT) were superior to sequential therapy or RT alone for achieving local and regional control when applied to stage 3 or stage 4 laryngeal cancer with T2, T3, or "low-volume" T4 tumors.[2] The authors concluded that RT with concurrent chemotherapy should be considered the standard of care for patients desiring laryngeal preservation whose cancers were within the categories of disease studied in the

trial. They further concluded that laryngectomy should be performed only as a salvage therapy. Finally, the most unsubstantiated conclusion: "we believe that in most patients with laryngeal cancer that the disease can be managed without a primary surgical approach."[2]

On the basis of these 2 studies, most medical centers in the United States now advocate the use of concurrent chemotherapy and RT for advanced laryngeal cancer, in the hope of preserving the larynx and not decreasing overall survival. Some patients truly have benefited from this approach—unfortunately, many others have not.

RESULTS OF THE CURRENT STANDARD OF CARE

It is now time to critically examine the results, unintended consequences, and continuing problems with the adoption of this management plan as the true "standard of care."

Specific Problems. What are the main concerns? The first is that survival has not stayed the same as with prior treatment strategies—it has decreased. The larynx is now the only organ for which cancer survival in the United States is worsening, not improving.[3] In September 2006, Hoffman et al[3] first reported that during the past 2 decades, overall cancer survival improved for all locations except the larynx. During that time, nonsurgical management of laryngeal cancer increased. Most notable was the finding of decreased survival for patients with advanced-stage laryngeal glottic cancer, early-stage supraglottic cancers, and supraglottic cancers classified as T3N0M0. For T3N0M0 laryngeal cancers at all sites, the 5-year relative survival was best with surgery and RT (65.2%).[3]

Even more recently, a December 2007 study by Chen and Halpern[4] reported the National Hospital-Based Cancer Registry data. Total laryngectomy was associated with increased survival compared with RT or with chemotherapy + RT ($p < .001$). This result was especially apparent for stage 4 disease. Patients with total laryngectomy had significantly greater survival than patients having chemoradiotherapy or RT alone for T4 cancers. For T3 laryngeal cancers, chemotherapy and RT significantly increased the risk of death compared with total laryngectomy alone (hazard ratio, 1.18; $p = .03$). These 2 studies[3,4] suggest that physicians should exercise caution when extrapolating the results of highly selected trials to a general, broad-based population.

Another unintended consequence is that laryngeal conservation surgery, as an option for many advanced laryngeal cancers, is now rarely discussed with the patient. Endoscopic and open partial laryngectomy procedures that have provided laryngeal preservation, good function, and often superior oncologic results are being abandoned in the United States. A corollary to this is that knowledge and skill of residents and fellows in head and neck laryngeal oncologic surgery are decreasing. Procedures such as open partial vertical laryngectomies, supraglottic laryngectomies, supracricoid operations, and transoral laser or robotic surgery gave patients functioning larynxes and superb oncologic results. However, the excellent results from managing advanced laryngeal cancer with these approaches are being seen less often in this country because of the decrease in resident training and experience in laryngeal conservation surgery.

Complications from chemotherapy and RT that once were rare are now more common and can be severe. Local tissues often do not heal after chemotherapy and RT. Significant pharyngeal and esophageal edema and stenosis are common; some cases are so extensive that the stenosis is complete and permanent. Patients requiring a total laryngectomy for salvage have more complications and increased fistulization risks that are rarely seen in the management of cases with initial total laryngectomy or after RT. In these cases, surgeons must now use hyperbaric oxygen, multiple flaps, and prolonged treatment modalities, and often still cannot correct the problems.

Delayed adverse effects from chemotherapy and RT to the head and neck area are also beginning to be seen. This was first noted many years after patients received treatment for nasopharyngeal cancer. In some, significant atherosclerosis of the carotid vessels has developed, and others have had delayed pharyngeal fibrosis and stenosis with a progressive inability to swallow and a risk of aspiration. The most serious finding has been the development of multifocal cancers in the treatment area. These occurrences require close monitoring in the future to determine their true frequency.

Prolonged treatment programs with increased costs are now the rule. Cost has many

components such as cost to the patient in time for treatment, lost work, and follow-up visits and procedures. The initial cost of the treatment program and all costs throughout the follow-up period must be considered. An accurate analysis of the total cost for chemotherapy and RT has not been done, but the initial treatment cost is much higher than that for treatment with surgery alone or surgery and postoperative RT.[5]

Summary of Unintended Consequences. Many patients are being denied treatment options. Surgical options are being decided by people who may not perform laryngeal conservation procedures. Many truly believe that there is no harm to the patients by first trying chemoradiotherapy and, if that fails, then using total laryngectomy as surgical salvage. Some patients have done well with this philosophy, but we are now seeing survival for laryngeal cancer decreasing, costs increasing, and many untoward consequences, based on a strategy of laryngeal preservation at all cost. The hoped-for results have not occurred. Patients are likely being counseled to receive chemoradiation for tumors or other criteria that were never part of the original patient selection group, and these selection criteria are also suspect.

The main questions now are "What happened?"; "What were the factors that led to these unintended consequences?"; "How can we avoid this in the future, and what should change now?"

WHAT HAPPENED?

What elements of the previous studies[1,2] led to the above-mentioned unintended consequences and problems with the current standard of care?

Selection Bias. The previously mentioned VA and RTOG 91-11 studies[1,2] took place in multiple centers over many years. The RTOG 91-11 study averaged only a few cases per year per center, which led to obvious concern about selection bias in these cases.[2] In the United States, advanced laryngeal cancer encompasses a greater number of glottic than supraglottic carcinomas, yet the RTOG 91-11 series consisted of predominantly supraglottic tumors (68%).

Questionable Treatment for Mobile Vocal Cords. Another major issue in the studies that led to the practice changes[1,2] was that all patients were said to have "advanced-stage" laryngeal cancer that required total laryngectomy. However, it is very unusual to recommend a total laryngectomy for a patient with mobile vocal cords, a good performance score, and the absence of prior RT. Almost half the patients in the 2 studies had mobile vocal cords—48% in the VA study[1] and 42% in the RTOG 91-11 study[2]—and would not have needed a total laryngectomy anyway. A certain percentage of patients with T4 tumors (10%) in the study groups also would have had mobile cords because the staging criteria at the time of the RTOG 91-11 study would have included supraglottic tumors that extended to the tongue base without involvement of the vocal cords.[2]

The literature contains numerous articles describing the excellent oncologic and functional outcomes for T1, T2, and T3 laryngeal cancers after the removal of portions of the larynx via the transoral or external route, for cancers that do not fix the arytenoid cartilage.[6–10] Unfortunately, because patients with these cancers were combined with those who had cordal fixation, we do not know the results of chemoradiotherapy for the subgroup of patients with true cordal fixation. This information is needed. One European study comparing treatment modalities for patients with fixed cord cancer was stopped because of the poor results of chemotherapy and RT compared with total laryngectomy.[11] The oncologic results for total laryngectomy in cases of fixed cords or T4 cancers are excellent.[12]

Unclear Definition of "Advanced" Disease. Great confusion remains with regard to the definition of "advanced" laryngeal cancer. The definition of advanced laryngeal cancer has become ambiguous, such that "advanced" equates with laryngectomy as the only surgical option. However, "advanced" now includes T4 tumors and also multiple T2 and T3 tumors and T4 laryngeal cancers with mobile vocal cords. Confusion arose as a result of the RTOG 91-11 report, with the introduction of a term not previously used in staging criteria: "*low-volume*" T4 cancer.[2] This was described by the authors as a tumor that came just into the thyroid cartilage or just through the thyroid cartilage. It is easy to see how physicians would not be able to clearly distinguish "low-volume" T4 tumors from classic

T4 tumors. The extrapolation of the methods of these studies to any patients with T4 tumors may have led to the poorer results being seen today. Does "advanced" refer to T stage or overall stage? Overall stage and T stage are often confused for each other; stage 3 and stage 4 or T3 and T4 are often taken to mean "advanced," and "advanced" implies laryngectomy.

A supraglottic cancer with mobile vocal cords and imaging that suggests extension into the preepiglottic space is a T3 cancer and, if N0, a stage 3 tumor. A T2 supraglottic cancer with 1 neck node noted on clinical examination is also stage 3. Both of these patients have mobile cords and "advanced" laryngeal cancer. If the examining physicians do not perform laryngeal conservation procedures, they may conclude that a total laryngectomy is necessary to surgically treat the cancer. In actuality, a transoral or open procedure could be done with excellent oncologic and functional results and no need for a total laryngectomy.[13] Inclusion of cases such as these in a series of "advanced" tumors would skew the results for patients with vocal cord fixation or T4 cancers.

Health and Age of Patients. Another concern with these studies[1,2] is the general health of the patients selected. More than 80% had Karnofsky performance scores >90. The typical patient with advanced laryngeal cancer is a heavy smoker and drinker, with multiple comorbid conditions and a poorer performance score. Extrapolation of the study recommendations to patients with laryngeal cancer and a poorer performance score could lead to more complications and deaths from treatment. Even with a good performance score, only 70% of the participants were able to finish the planned concurrent treatment, and 5% of the patients died from the treatment. This treatment-related mortality is much greater than that after surgery and RT. Surgical management of disease for patients with even substantial medical problems would have a treatment-related death rate of <1%. Our aging population is also a concern; patients >70 years old have a harder time tolerating chemoradiotherapy, and the prior studies included few patients from this age group.[14] Applying the results from these studies to patients >70 years old could also explain the poorer results now being seen.

Acceptance of a 5% death rate from chemoradiotherapy has been justified by the finding of a low rate of distant disease. However, some of the main factors associated with the presence of distant disease are high-volume neck disease, metastasis to low nodes, or both. In the RTOG 91-11 study, 73% of the patients had low-volume neck disease, either N0 or N1.[2] This is surprising, given the high number of supraglottic cancers and the tendency for significant cervical metastasis to occur with advanced supraglottic cancers. The noted low incidence of distant metastasis may have been a result of the selection of patients with low-volume neck disease.

Toxicity and Unknown Deaths. Another factor associated with the decrease in survival for patients with laryngeal cancer who received chemoradiotherapy may be the toxicity of the treatment. Substantial toxicity was associated with chemotherapy and RT; 82% of patients had stage 3 or stage 4 toxicity. Another concern about the RTOG 91-11 series was the high death rate from unknown causes noted during follow-up.[2] This may have arisen from secondary aspiration, pneumonia, or other unrecognized sequelae of treatment.

Summary of What Happened. The main problems with the 2 previous reports[1,2] are that they studied few cases from multiple centers, included a disproportionate number of supraglottic tumors and a high percentage of patients with mobile cords, and 1 used the confusing inclusion criterion of "low-volume" T4 tumors. Moreover, in general the patients were young, in very good health, and had minimal neck disease. No information was given regarding the results of chemoradiotherapy in patients with fixed cord tumors. All of the above can lead to errors when the recommendations of these studies are used to treat most people with advanced laryngeal cancer. Applying the study recommendations to a population of older, sicker patients and to more patients with fixed cord tumors and T4 tumors may have led to the poorer results being seen today.

WHAT CAN BE DONE TO AVOID SIMILAR EVENTS IN THE FUTURE?

First, several factors must be considered when evaluating randomized controlled trials. To determine evidence-based clinical practice guidelines, practitioners often rely on published

results of multi-institutional trials. These trials may provide evidence to show that a recommended treatment is effective and beneficial for improving a health outcome. However, for correct interpretation and use of the methods, the results must be applicable to the general medical community. If the results from highly controlled multi-institutional studies are not transferrable to a community practice, use of the recommended treatment may result in inadvertent harm to patients, and the value of the trial will not be realized. The true determination of value must take into account quality, outcomes, satisfaction, and cost.[15]

Other elements that should be required in reports of trials are the functional results of the organ affected. Laryngeal preservation alone should not be the goal when choosing a treatment. "Preservation of a larynx" must be reported because it relates to functional preservation—speech, swallowing, and breathing—not just organ preservation. The short-term and long-term effects of chemotherapy and RT on patient requirements for temporary or permanent nasogastric, gastrostomy, and tracheotomy tubes have not been consistently reported in published articles; these outcomes must be accurately stated. Surgical interventions required over time to maintain a functioning pharynx must also be included in the treatment analysis.

Prior studies reviewing speech-related quality-of-life scores found results for patients receiving chemoradiotherapy for laryngeal preservation similar to those for patients who had a laryngectomy.[16] Patients still communicate after total laryngectomy by tracheoesophageal puncture, by esophageal speech, or via the use of an electronic larynx. The general quality-of-life domains for those who undergo chemoradiotherapy are similar to those for patients who undergo surgery and RT.[17] After total laryngectomy, the presence of a stoma adversely affected life more than did an alteration in voice.[18] We must also look at other quality-of-life results of treatment, such as pain, social interactions, complications, length of treatment, and patient well-being.

Other requirements for avoiding future adverse events in the area of advanced laryngeal cancer are that, as mentioned earlier, we need a consensus with regard to the definition of "advanced" disease. We must understand the oncologic results, overall survival, cancer-related survival, local/regional recurrence, and distant disease. Finally, costs are important, both the initial costs and total costs throughout the patient's cancer management.

WHAT SHOULD BE DONE?

Individualized Medicine. The complexity of laryngeal cancer warrants an individualized approach to the management of this disease. Numerous patient factors must be considered: age, comorbid conditions, functional status, presence of risk factors, prior treatment, laryngeal anatomy, and the patient's wishes. Tumor factors include location of the tumor, its extent, its growth characteristics, either ulcerative or exophytic, and its behavior in the host. Pathologic factors to consider are the grade of the tumor, the subtype of the tumor, the presence of angiolymphatic invasion, the presence of nodal disease, and whether extracapsular disease or desmoplasia is present. Finally, physician factors must be considered, such as experience, training, philosophy, presence or absence of support personnel and equipment, and willingness to accept lifelong patient responsibility. A joint treatment plan should be determined by the patient and his or her physician(s).

Treatment Recommendations. How does an individualized approach to laryngeal cancer work? What treatments can be recommended for which disease types? What is a rational plan? The main indications for total laryngectomy in my practice are (1) failure of either RT or RT + chemotherapy and (2) for management of T4 cancers. All treatment modalities are important. For successful management of advanced head and neck cancer, multimodality treatment is usually necessary.

Patients with T4 cancer require total laryngectomy or extended total laryngectomy. It is very difficult for practitioners to try to distinguish low-volume T4 tumors from T4 tumors on the basis of examination or imaging studies; this has not worked and is unproved. Tumors that extend through the laryngeal cartilage should be treated with total laryngectomy. On the basis of primary tumor pathologic findings and extent of neck disease, a decision can be appropriately made whether to use postoperative RT or chemoradiotherapy.

Patients with T3 cancers and mobile arytenoids have numerous surgical conservation

options that provide excellent oncologic results, preserve laryngeal function, and do not require a total laryngectomy. The option of RT or RT + chemotherapy can also be offered. For T3 cancers with fixed arytenoids or true cordal fixation, the best form of treatment is still not known. For these patients, chemotherapy and RT with close follow-up is often proposed. Honest and frank discussion with the patient concerning the unknowns is required, however, and some will choose to proceed with a total laryngectomy or, rarely, a subtotal laryngectomy. A randomized trial of patients with true vocal cord fixation is required to answer the question of the oncologic, functional, and long-term benefit of chemotherapy and RT versus surgery and postoperative RT.

For T2 and T1 laryngeal cancers, many different surgical conservation procedures can be used by experienced surgeons. Frozen section pathologic analysis is essential, and the ability to operate transorally and via an open approach gives excellent functional and oncologic results with laryngeal preservation. RT is also an option for these cases.

Prevention and early diagnosis are equally important. We must continue our efforts in encouraging patients to stop smoking because these cancers can be prevented. We must also not forget that the best results are seen when laryngeal cancers are treated early; these tumors can be cured.

CONCLUSION

It is time to reexamine the management of laryngeal cancer. Other authors have raised concerns similar to those discussed here.[19,20] The broad-based application of recommendations from highly controlled, multi-institutional studies with carefully selected patients can be problematic and may lead to unintended consequences. The inclusion of patients with cancers that are less than truly "advanced" can skew the treatment results. It is easy to see how unwarranted conclusions from these studies may lead practitioners to apply treatment recommendations to patients who were not within the studies' selection parameters. Long-term follow-up is essential, and all aspects of a selected treatment modality need to be reported.

Foote et al[21] proposed that surgeons operate for their ego, to increase their case numbers, to justify or acquire staff and equipment, or for monetary gain; in actuality, surgeons care very much about their patients and want to offer the most effective form of therapy. However, we all need to better understand the full scope of the current management of laryngeal cancer. This commentary has focused on the unintended consequences that have occurred as a result of unwarranted conclusions. The studies have been conducted with good intentions. Many patients have a preserved larynx, good function, and no signs of recurrence or complications today after receiving chemotherapy and RT. However, we need to better identify who these patients are and why their therapy was effective—we cannot continue on the present course. Survival after laryngeal cancer should be improving, not decreasing.

REFERENCES

1. Wolf GT, Hong WK, Gross Fisher S, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer (The Department of Veterans Affairs [VA] Laryngeal Cancer Study Group). N Engl J Med 1991;324:1685–1690.
2. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349: 2091–2098.
3. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. Laryngoscope 2006;116 (Suppl 111):1–13.
4. Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 2007;133:1270–1276.
5. Davis GE, Schwartz SR, Veenstra DL, Yueh B. Cost comparison of surgery vs organ preservation for laryngeal cancer. Arch Otolaryngol Head Neck Surg 2005;131:21–26.
6. Agrawal A, Moon J, Davis RK, et al. Southwest Oncology Group. Transoral carbon dioxide laser supraglottic laryngectomy and irradiation in stage I, II, and III squamous cell carcinoma of the supraglottic larynx: report of Southwest Oncology Group Phase 2 Trial S9709. Arch Otolaryngol Head Neck Surg 2007;133:1044–1050.
7. Hinni ML, Salassa JR, Grant DG, et al. Transoral laser microsurgery for advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 2007;133:1198–1204.
8. Lefebvre JL. Laryngeal preservation in head and neck cancer: multidisciplinary approach. Lancet Oncol 2006;7: 747–755.
9. Rassekh CH, Weinstein GS, Laccourreye O. Supracricoid partial laryngectomy. In: Bailey BJ, Calhoun KH, Deskin RW, et al, editors. Head and neck surgery: otolaryngology, 2nd edition, Vol. 2. Philadelphia: Lippincott-Raven; 1998. pp 1805–1815.
10. Steiner W. Results of curative laser microsurgery of laryngeal carcinomas. Am J Otolaryngol 1993;14:116–121.
11. Richard JM, Sancho-Garnier H, Pessey JJ, et al. Randomized trial of induction chemotherapy in larynx carcinoma. Oral Oncol 1998;34:224–228.
12. DeSanto LW. T3 glottic cancer: options and consequences of the options. Laryngoscope 1984;94:1311–1315.

13. Lefebvre JL. What is the role of primary surgery in the treatment of laryngeal and hypopharyngeal cancer? Hayes Martin Lecture. Arch Otolaryngol Head Neck Surg 2000;126:285–288.
14. Bourhis J Sr, Le Maitre A, Pignon J, et al. Impact of age on treatment effect in locally advanced head and neck cancer (HNC): two individual patient data meta-analyses. J Clin Oncol 2006;24 (Suppl 18S):280s (abstract).
15. Tunis SR. Reflections on science, judgment, and value in evidence-based decision making: a conversation with David Eddy. Health Aff 2007;26:w500–w515.
16. Major MS, Bumpous JM, Flynn MB, Schill K. Quality of life after treatment for advanced laryngeal and hypopharyngeal cancer. Laryngoscope 2001;111:1379–1382.
17. Hanna E, Sherman A, Cash D, et al. Quality of life for patients following total laryngectomy vs chemoradiation for laryngeal preservation. Arch Otolaryngol Head Neck Surg 2004;130:875–879.
18. DeSanto LW, Olsen KD, Perry WC, Rohe DE, Keith RL. Quality of life after surgical treatment of cancer of the larynx. Ann Otol Rhinol Laryngol 1995;104:763–769.
19. Genden EM, Ferlito A, Rinaldo A, et al. Recent changes in the treatment of patients with advanced laryngeal cancer. Head Neck 2008;30:103–110.
20. Weinstein GS. Organ preservation surgery for laryngeal cancer: the evolving role of the surgeon in the multidisciplinary head and neck cancer team. Oper Tech Otolaryngol Head Neck Surg 2003;14:1–2 (editorial).
21. Foote RL, Brown PD, Garces YI, Okuno SH, Miller RC, Strome SE. Informed consent in advanced laryngeal cancer. Head Neck 2007;29:230–235.

COMMENTARY

REEXAMINING THE TREATMENT OF ADVANCED LARYNGEAL CANCER: THE VA LARYNGEAL CANCER STUDY REVISITED

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I am pleased to be asked to comment on the thoughtful editorial submitted by Dr. Kerry Olsen. In his treatise, Olsen calls for a reevaluation of the treatment of patients with advanced laryngeal cancer based on published reports of changing patterns of care and survival outcome for patients with laryngeal cancer. Two recent reviews of retrospective data from the National Cancer Data Base (NCDB) form the basis for his concerns because they have suggested that modest declines in overall survival rates for patients with laryngeal cancer may be ascribed to the increasing use of nonsurgical management.[1,2] His premise is that published results of recent, randomized trials[3,4] of chemoradiation treatment that have demonstrated high levels of successful larynx preservation have had the unintended consequence of denying some patients beneficial surgery and have led to a national decline in overall survival rates. Although his comments are factual and his concern is justified, I believe his interpretation of

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the NCDB data analyses is incomplete and falls far short of supporting his conclusions.

THE FACTS

We should examine the facts. It is a fact that neither randomized trial of organ preservation in advanced laryngeal cancer (Veterans Administration [VA] Larynx Study or Radiation Therapy Oncology Group [RTOG] 91-11) demonstrated improved survival with nonsurgical treatment. Both studies offered new chemoradiation strategies as "alternative" treatment approaches that had potential functional and quality of life benefits in the form of laryngeal preservation. In fact, the VA study—which had a surgery and postoperative radiation control arm—showed a nonsignificant 5% decrease in overall survival at 5 and 10 years for the nonsurgical group that was not significant and was counterbalanced by larynx preservation in two thirds of patients. This decrease, though, is similar to the overall decrease in survival reported in Hoffman's study.[1]

It is a fact that the NCDB study documents a change in treatment patterns with an increase in the use of chemoradiation from 3% of cases in 1990 to 12% of cases in 2000, with the greatest increases not occurring until 1996.[1] However, the same study also documents an increase in local tumor excision from 12% in 1991 to >20% in 2001 and an increase in "no surgery" treatment (which would include mostly radiation alone) from 45% in 1991 to 56% in 2001. It is a fact that when nonsurgical treatment is further analyzed and radiation alone is separated from chemoradiation, the radiation-alone group has the worst survival compared with that of both surgery and chemoradiation. A similar finding was reported by Chen and Halpern,[2] who stated that "in contrast to the significantly decreased survival with radiation alone, the odds of mortality were not significantly different between patients with stage III disease receiving chemo-RT vs those receiving TL ($p = .09$)." For the largest subgroups analyzed by Hoffman et al,[1] the differences between surgery and radiation versus chemoradiation were less dramatic. In fact, it is clear that even though there was a 5% overall difference in outcome in favor of surgery and radiation for the entire T3 group, a significant difference was found only in comparing surgery (± radiation) to radiation alone ($p < .05$), with no statistically significant difference between surgery alone or surgery plus radiation compared with chemoradiation ($p = .503$ and $p = .067$, respectively). Olsen fails to acknowledge that the large subgroup of glottic T3N0 patients showed identical observed and relative survival rates (54.7% and 65.6%, respectively) for surgery and radiation versus chemoradiation. Further, for the supraglottic T3N+ and T4N0 subgroups, survival rates actually improved overall over the 1990 to 1996 time period when the first increases in use of chemoradiation therapy were noted. The most striking declines in survival for supraglottic cancer patients were actually seen among patients in the early stage who would not have received chemoradiation.

WHAT IS THE STANDARD OF CARE?

Randomized clinical trial evidence for treatment advances has been the gold standard leading to changes in cancer therapy. It is true, however, that how the results of such carefully conducted controlled trials are interpreted, applied by the community at large, and influenced by both physician and patient bias, can have "unintended consequences." Olsen's commentary suggests that chemoradiation approaches are inappropriately being used and are resulting in cure rates that are inferior to historical rates for total laryngectomy. He further implies that many such patients could benefit from conservation laryngeal procedures if only surgeons were given that chance. Of course, there are no randomized trial data showing superior or even equivalent cure rates for "organ preserving" surgery versus total laryngectomy. Treating physicians must always question, evaluate, and refine their treatment recommendations as part of the dynamic process of medical progress and, thus, it is *always* appropriate to reexamine treatment results. One of the main reasons that advanced laryngeal cancer is the subject of this commentary is because there are several therapeutic choices facing patients and how therapeutic choices are presented to patients can influence treatment selection. Many factors contribute to these treatment decisions. Olsen offers concerns regarding some of these factors and questions how they may be inappropriately favoring nonsurgical methods. When survival results are similar among differing oncologic approaches, therapeutic decision making must be based on both

patient and physician perceptions of quality of life, potential complications of therapy, and expected functional results. When substantial differences in survival rates are lacking, these secondary factors become important in defining what treatments are acceptable under current "standards of care."

In fact, no organ-preserving treatment (either surgical or nonsurgical) has shown better overall survival rates than total laryngectomy. The current "standard of care" includes several options. In 2006, a panel of experts was organized by the American Society of Clinical Oncology to extensively review the literature and develop evidence-based clinical guidelines for larynx-preservation strategies.[5] The results of that review clearly state that "evidence supports the use of larynx-preservation approaches for appropriately selected patients without a compromise in survival; however, no larynx-preservation approach offers a survival advantage compared with total laryngectomy and adjuvant therapy with rehabilitation as indicated."[5] This comprehensive review recommended organ-preserving surgery as an option, particularly for patients with T1 or T2 disease. The reviewers affirmed that for most patients with T3 or T4 disease without tumor invasion through cartilage into soft tissues, a larynx-preservation approach is an appropriate, standard treatment option, and that concurrent chemoradiation is the most widely applicable approach.[5] It is not accepted that concurrent chemoradiation is the only standard of care, but an acceptable alternative to sequential chemoradiation or to total laryngectomy since concurrent chemoradiation has not been directly compared with total laryngectomy.

Therapy selection begins with what is the best treatment for cure and is modified by the function sparing goals. The differences in function and quality of life are very apparent for advanced laryngeal cancer in which patients face total laryngectomy and less apparent when conservation laryngectomy is feasible. So, why would anyone consider chemoradiation the new "standard of care"? There is no evidence (other than our own phase II data[6]) that any chemoradiation paradigm yields better survival rates than those of total laryngectomy. In fact, the term "standard of care" can be applied to chemoradiation for advanced laryngeal cancer only when the goal of treatment is "laryngeal preservation." Chemoradiation and even radiation alone are considered alternatives to total laryngectomy in that setting, and the relative merits of each are measured on the basis of a variety of variables including cure rates, toxicity, function, and success of salvage treatments.

Dr. Olsen correctly observes that the results of the 2 large prospective, randomized trials have introduced new therapeutic options for patients facing total laryngectomy. The results of these trials have been widely disseminated and embraced by medical and radiation oncologists worldwide and less warmly received by surgeons who are often called on to treat recurrent disease after failed chemoradiation. Such secondary surgery can be ineffective if not performed in a timely fashion and may yield inferior overall survival rates, as demonstrated in the surgical analysis of the RTOG 91-11 trial.[7] In the carefully monitored VA trial that incorporated early surgical salvage, patients with failed chemotherapy who underwent total laryngectomy had survival rates identical to those of the patients having successful organ preservation.

The evolution of these combined approaches clearly offers an alternative to immediate total laryngectomy and not a substitute for surgery as a standard treatment. In fact, the more recent patterns of care study by Chen and Halpern[2] shows that even in 1998, the majority of patients (53.6%) with advanced laryngeal cancer underwent total laryngectomy as their treatment. An earlier study of patterns of care using the NCDB by this group demonstrated that there was a significant increase in the use of chemoradiation, although this increase was accompanied by a greater decrease in the use of radiation alone than a decrease in use of total laryngectomy. The use of partial and other laryngeal surgery also increased in the 1985 to 2001 period.[8] Hence, the data do not support a replacement of surgery as a standard of care. In every instance, treatment should be personalized to the needs and desires of the patient and the therapeutic expertise of the treatment team. To do otherwise is truly to deny your patient a "standard of care."

UNINTENDED CONSEQUENCES?

Let's look at some of the other arguments for reconsidering surgical approaches. Dr. Olsen's passionate call for a reassessment is based on a number of facts, including: (1) the data analysis

of changes in survival and treatment patterns for laryngeal cancer that implies that the introduction of chemoradiation approaches was responsible; (2) the observation of increased complications from chemoradiation that compromise function and quality of life even when the structure of the larynx is preserved; (3) the inability to identify patients who would benefit most from either the surgical or the nonsurgical approach; and (4) surgical experiences showing that secondary surgery in the setting of failed chemoradiation can lead to increased complications and potentially decreased survival. Careful, dispassionate, and unbiased analysis of each of these issues is necessary.

The primary problem that Olsen identifies to support his call to abandon chemoradiation is the previously identified decline in survival rates. Olsen cites the Hoffman et al[1] study that analyzed Surveillance, Epidemiology, and End Results Program (SEER) data from the NCDB. That report examined treatment modalities, tumor stage, tumor site, and outcome over the period from 1985 to 2001. An approximate overall 5% decrease in observed (actual) and relative (actual survival divided by expected survival adjusting for age, sex, and gender) survival rates was reported for all patients. The greatest decrease in survival was noted in the period 1985 to 1990 (prior to publication of the results of the VA or RTOG Studies) and the 1994 to 1996 period. Olsen fails to observe that the lowest survival rates were reported in 1993, well before many practitioners adopted chemoradiation approaches. In comparing 1985 with 1996, there was only a 5% decrease in survival and it was observed across all stages of cancer; 60% of patients analyzed were treated for T1 and T2 cancers for which chemoradiation would not typically be used. Other factors could be implicated in this overall decline and were not cited by Olsen. The analysis of changes in patterns of treatment included only cases diagnosed prior to 1997. It is interesting to note that there was a significant decrease in the use of radiation alone and an increase in the use of surgery and radiation in the years 1987 to 1991. This period corresponds to one of the greatest declines in cure rates when the increase in use of chemoradiation went from only 2% to 4%. The decline in the use of surgery and radiation did not start until 1991 and was paralleled by a large decrease in the use of surgery alone and an increase in the use of "other specified treatments." In fact, there was a dramatic increase in the frequency of "local tumor resection" from 7% to 21% in this time interval. It is equally possible that the later declines in larynx survival rates were related to these changes in therapy choice than to widespread use of chemoradiation. Concluding that the changes in overall survival were solely the result of increasing use of chemoradiation does not explain the major decreases in survival for stage I and stage II cancers, particularly for supraglottic sites since these patients are not typically treated with chemoradiation. During the reporting period, it would have been inconceivable to treat such patients with chemoradiation outside of a carefully designed clinical trial. Rather, the survival changes noted by Hoffman et al[1] are just as likely to arise from ineffective treatment with radiation alone or perhaps increasing use of endoscopic local resection techniques for management of these cancers.

For the subset of T3N0M0 patients, a 4.7% difference in survival was reported between surgery and radiation versus chemotherapy and radiation. However, when radiation alone is included, the differences between surgical and nonsurgical treatment results in a dramatic difference in favor of surgery. Olsen fails to note that these poor results with "nonsurgical treatment" primarily arise from including radiation-alone treatment that achieved only a 33% relative survival rate. Moreover, he mentions the favorable observed and relative survival rate of 65% for surgery during the 1994 to 1996 interval but fails to mention that this rate is identical to the chemoradiation results for the same time period. The overall frequency of chemoradiation as a treatment modality was minor and increased from 2% in 1987 to only 7% in 1996. The use of endoscopic and other conservation surgical approaches could not be analyzed for these periods because of inadequate data reporting. Careful analysis of these combined data does not clearly support the superiority of surgical management over chemoradiation.

Dr. Olsen also cites the report by Chen and Halpern[2] that analyzed more recent hospital cancer registry data for patients with advanced cancers to investigate the hypothesis that declining survival rates are occurring in patients with advanced laryngeal cancer and are attributed to the increasing use of chemoradiation. Chen examined recent hospital records

from 1995 to 1998 and confirmed that more than half of all patients were treated with total laryngectomy, 31% with radiation alone, and only 16% with chemoradiation. These data hardly reflect adoption of chemoradiation as the new "standard of care." Their analysis also confirms the poor survival rates with radiation alone, with a 60% increased risk of death for patients treated with radiation alone. They also reconfirm that there were no differences in survival between total laryngectomy and chemoradiation for stage III patients. Not surprisingly, for patients with stage IV disease, better survival was achieved with total laryngectomy. It was for this reason that the RTOG 91-11 study excluded T4 patients since one of the treatment arms was radiation alone.

Dr. Olsen offers the opinion that an "unintended consequence" of the increase in use of chemoradiation is our failure to consider or discuss conservation laryngeal surgery as an option to total laryngectomy for patients with stage III or stage IV cancers. He may be correct, since few surgeons have the experience or expertise to properly select patients or perform these demanding and precise procedures. He incorrectly assumes that cure rates for organ-preserving surgery in advanced laryngeal cancer are superior to those for chemoradiation in properly selected patients. At least one prospective study by the Southwest Oncology Group with long-term follow-up showed that the introduction and use of endoscopic supraglottic resections for patients with early (T1,T2) cancers—even with the addition of postoperative radiation—were associated with a dismal 5-year progression-free survival rate of $<60\%$.[9] Even in the VA Larynx trial, in which supraglottic laryngectomy was permitted for very select lesions, the survival rate for the few patients treated with the supraglottic conservation technique were terrible and substantially less than that for total laryngectomy (unpublished data). The specialized skills necessary to administer high-quality chemotherapy and radiation are no different from the need for specialized skills for surgeons performing conservation procedures. Neither treatment approach can be simply and successfully translated to community practitioners who may lack adequate or appropriate experience. Support for this contention is provided by recently demonstrated improved survival rates for laryngeal cancer when patients are treated in high-volume teaching centers.[10] If patients are being denied surgical treatment options, it is our fault as counseling physicians. We cannot shift the blame for this to other oncologists or to randomized trial results.

We are in agreement with Olsen that larynx preserving chemoradiation should be limited to patients facing total laryngectomy. He comments that the costs associated with chemoradiation are high, and he is correct. Any time redundant treatment is necessary, costs will be unacceptably high. However, it is a fact that few patients ever return to gainful employment after total laryngectomy, whereas returning to productive employment is more likely after chemoradiation. The societal benefit in such cases would likely outweigh the increased cost of such organ-preservation treatment.

Dr. Olsen focused on unintended consequences—but what were the intended consequences of this paradigm shift? The first goal of chemoradiation strategies was to avoid total laryngectomy in a subset of patients with cancers sensitive to chemotherapy and radiation. The VA study used tumor response to neoadjuvant chemotherapy as a biomarker to select such patients. That study and many that followed are remarkably consistent in identifying 65% to 70% of patients with radiation-sensitive tumors that can avoid total laryngectomy. This is regardless of increasingly intensive chemotherapy and radiation regimens that add toxicity only in the form of mucositis, fibrosis, laryngeal edema, and often long-term tracheostomy and/or feeding tube. We have identified the presence of a feeding gastrotomy as the most significant predictor of poor quality of life rather than the presence of a tracheostome[11] and that quality of life related to speech was similar among long-term survivors of laryngeal cancer regardless of total laryngectomy or larynx preservation.[12] These findings should raise legitimate concerns about embracing increasingly intensive treatments with escalating toxicity when such therapy is not accompanied by improving patient selection or cure rates. There is thus a consistent group of 30% to 35% of patients that may require or even benefit from primary surgery. The approach we have taken at Michigan has been to use the consistent biomarker of response to neoadjuvant chemotherapy to select patients for surgical management. With this approach we have achieved a remarkable long-term cause-specific survival rate of 87% in a nonselected consecutive series of patients with stage III/IV laryngeal cancer.[6]

Dr. Olsen implies that the results of the randomized VA study should be questioned because of selection bias. He states that 48% of patients entered in the VA study had mobile vocal cords and perhaps did not require total laryngectomy. The VA patients were not highly selected except that they had to be facing total laryngectomy with the exception of a very few who had tumors amenable to conservation supraglottic resections. Only 12% of patients (20/166) randomized to surgery were clearly eligible for conservation laryngectomy and, as described previously, the outcome was not good for this group. In each instance, approval for the conservation approach had to be given by the study chairman. Most patients in the trial had very advanced disease, with 24% requiring preoperative tracheostomy for airway intervention.

Interpretation of subset analyses from such randomized trials are fraught with hazard, and thus the many subset analyses that were performed on the VA trial data were not published. However, several are worth mentioning here. There were no differences in survival by T classification among the treatment arms. Larynx-preservation rates were similar for glottic and supraglottic sites, but were lower for patients with T4 cancer and did not differ significantly with respect to either vocal cord paralysis or cartilage invasion. T3N0 and T4N0 patients had identical overall survival ($p = .7994$), although T4N0 patients treated with surgery had slightly better survival than T4N0 patients treated with chemoradiation ($p = .05$). We have recently confirmed excellent survival rates for T4 patients with cartilage invasion when early patient selection for salvage surgery is used as part of an organ-preservation strategy.[13]

Is chemoradiation of questionable value for patients with mobile vocal cords? Patient eligibility for the VA study required stage III or stage IV disease and excluded only T1N1 patients. Most of the patients had supraglottic cancers and thus many did not have vocal cord fixation but had regional metastases, with 28% with N2,3 disease. A total of 26% of the VA patients had T4 cancers. Olsen states that the oncologic results for total laryngectomy in cases of fixed cord or T4 cancer are excellent. The Mayo Clinic's own 1985 historical series of results for surgical treatment of supraglottic cancers, including T1 and T2, reports a survival rate of only 55%, and a retreatment rate of 46% in patients with N+ disease with only 46% of patients alive with larynx intact.[14] Further, it is very likely that the poor results for radiation alone identified in the Hoffman and Chen articles[1,2] stem from radiation alone being prescribed for cancers in patients with mobile vocal cords and not from the use of chemoradiation.

Dr. Olsen cites the possibility that the health and age of the patients treated with chemoradiation might result in poor results. He suggests that the health of the VA patients was better than that seen in most community settings and that this explains why the differences with primary surgical management were not greater. Only 76% of the VA patients had Karnofsky performance status >80. It is true that poorer outcomes have been linked to lower socioeconomic status,[2,15] and recently better survival has been reported in high cancer volume teaching centers.[10] Patients in the VA study were aggressively screened but not highly selected. Of 639 patients screened, 48% were excluded primarily because of wrong tumor site or stage (23%), other or prior malignancy (21%), poor renal or cardiac status (22%), or patient refusal (20%). It has been shown in recent meta-analysis that there is limited efficacy for chemotherapy added to local treatment in patients >80 years of age.[16] The oldest patient in the VA study was 79 years old and the mean age of the patients was 62 years. Selection bias is much more likely to compromise interpretation of retrospective reports than prospective randomized trials such as the VA study. There are no randomized prospective trials of organ-preserving surgery. Because of precise limitations by tumor extent, patients selected for organ-preserving surgery are much more highly selected than patients treated with chemoradiation. There are no SEER Program data on conservation laryngeal surgery outcomes.

Olsen speculates further that decreasing survival rates in laryngeal cancer may result from toxicity and deaths from unknown causes among chemoradiation patients. Because the VA trial was randomized, it was easy to investigate differences in deaths from other causes comparing surgery with chemoradiation. There was no increase in treatment-related deaths in the patients randomized to chemoradiation compared with surgery. The frequency of treatment-related death on both treatment arms was 2%. Deaths from unknown or other causes made up 16% of deaths in both treatment arms. Thus, the randomized data do not support Olsen's contention that an observed decrease in survival

rates noted by Hoffman and colleagues might be ascribed to toxicity or to the use of chemoradiation in older, sicker patients with T4 disease or fixed vocal cords.

INDIVIDUALIZED MEDICINE

The history of laryngeal cancer treatment is characterized by multidisciplinary management and personalized care. Thus, the introduction of new treatment options is no excuse to abandon individualized care or to abandon surgical management. So I enthusiastically agree with Dr. Olsen that we must continuously reevaluate our treatment results, especially when so many new variables are being introduced to the decision making for treatment recommendations. We must be cautious when applying results from clinical trials to populations of patients not intended or appropriate to be treated with the study methods. This likely constitutes the "real" unintended consequences that Olsen is worried about. Poorly conceived treatment plans with inadequate involvement of surgical oncologists to monitor tumor response and success of treatment are likely to have poor results. In all organ-preservation approaches, surgical salvage is an integral part of the treatment strategy and, if not properly performed in a timely fashion, will yield survival rates inferior to published trial results. Randomized trial evidence still provides the least biased, most reliable data from which to draw conclusions. The excellent "oncologic" results with organ-preserving surgery that Olsen promotes were not based on prospective randomized trial data, but were derived from retrospective case series in highly selected patient populations treated by very experienced surgeons.

In summary, the evidence is clear that the management of laryngeal cancer is changing. The reasons for the modest decreases in NCDB survival reported by Hoffman et al[1] and Chen and Halpern[2] are not fully understood but appear across all stages of disease and seem more closely related to the use of radiation alone or local surgical resection as treatment modalities. The role of new conservation surgical procedures, including endoscopic resections, was not evaluated by Hoffman or Chen because of inaccurate or incomplete coding of treatment data. It may be equally likely that the increasing use of endoscopic techniques by unskilled surgeons may also be a contributing reason for these results.

I completely agree with Olsen's recommendations that we need to take an individualized approach to management decisions. We have always done that in a multidisciplinary fashion using the best information available to counsel our patients. This process has never been more challenging, given that additional variables are added, such as chemotherapy, robotics, and biomarkers, for instance. What is clear to me is that response to neoadjuvant chemotherapy is the strongest and most reliable biomarker that we have in advanced laryngeal cancer. We have previously demonstrated unachievable cure rates in patients with advanced disease using this biomarker to select patients for therapy. Because of these data and the results of randomized trials, it is impossible for us to go back to treating all patients with a surgical approach. We must continue to refine the specificity of our biomarkers and work to decrease the intensity of treatment in future protocols so as to achieve the best cure rates with the least toxicity.

REFERENCES

1. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care and survival. Laryngoscope 2006;116 (Suppl 11):1–13.
2. Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 2007;133:1270–1276.
3. Wolf GT, Hong WK, Gross Fisher S, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer (The Department of Veterans Affairs [VA] Laryngeal Cancer Study Group). N Engl J Med 1991;324:1685–1690.
4. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349: 2091–2098.
5. Pfister DG, Laurie SA, Weinstein GS, et al. American Society of Clinical Oncology Clinical Practice Guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. J Clin Oncol 2006;24:3693–3704.
6. Urba S, Wolf GT, Eisbruch A, et al. Single cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 2006;24:593–598.
7. Weber RS, Berkey BA, Forastiere A, et al. Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91-11. Arch Otolaryngol Head Neck Surg 2003;129:44–49.
8. Chen AY, Schrag N, Hao Y, et al. Changes in treatment of advanced laryngeal cancer 1985–2001. Otolarynogol Head Neck Surg 2006;135:831–837.
9. Agrawal A, Moon J, Davis RK, et al. Southwest Oncology Group. Transoral carbon dioxide laser supraglottic laryngectomy and irradiation in stage I, II, and III squamous cell carcinoma of the supraglottic larynx: report of Southwest Oncology Group Phase 2 Trial S9709. Arch Otolaryngol Head Neck Surg 2007;133:1044–1050.

10. Chen AY, Pavluck A, Ward EM. Improved survival of advanced laryngeal cancer is associated with treatment at high volume teaching facilities. Proc American Head and Neck Society, 2009 Annual Meeting, Phoenix, AZ (abstract SO22). May be accessed at http://www.ahns.info/meetings/documents/AHNS09FinalProgweb.pdf.
11. Terrell JE, Ronis DL, Fowler KE, et al. Clinical predictors of quality of life in head and neck cancer patients. Arch Otolaryngol Head Neck Surg 2004;130:401–408.
12. Terrell, JE, Fisher SG, Wolf GT, et al. The VA Laryngeal Cancer Study Group: long term quality of life after treatment for laryngeal cancer. Arch Otolaryngol Head Neck Surg 1998;124:964–974.
13. Worden FP, Moyer J, Lee JS, et al. Chemoselection as a strategy for organ preservation in patients with T4 laryngeal squamous cell carcinoma with cartilage invasion. Laryngoscope 2009;119:1510–1517.
14. DeSanto LW. Cancer of the supraglottic larynx: a review of 260 patients. Otolaryngol Head Neck Surg 1985;93:705–711.
15. Karvonen-Gutierrez CA, Ronis DL, Fowler KE, Terrell JE, Gruber SB, Duffy SA. Quality of life scores predict survival among patients with head and neck cancer. J Clin Oncol 2008;26:2754–2760.
16. Bourhis J Sr, Le Maitre A, Pignon J, et al. Impact of age on treatment effect in locally advanced head and neck cancer (HNC): two individual patient data meta-analyses. J Clin Oncol 2006;24(Suppl 18S):280s (abstract).

COMMENTARY

LARYNX PRESERVATION AND SURVIVAL TRENDS: SHOULD THERE BE CONCERN?

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The publication by Hoffman and colleagues[1] in 2006 of a trend for declining survival for laryngeal cancer based on retrospective cohort analyses of the National Cancer Data Base (NCDB) has led some to question the use of chemotherapy and radiation therapy (RT) to preserve the larynx as an alternative to total laryngectomy. This treatment paradigm evolved over >2 decades of prospective clinical trials research—proof of concept feasibility trials and then multi-institutional randomized controlled trials.[2–6] Carefully conducted clinical research has led to evidence-based incremental change in the practice of head and neck oncology and to a team approach of multidisciplinary patient management. A hallmark is the collaborative research among surgeons, radiation oncologists, and medical oncologists that enabled the current treatment options for patients with cancers of the larynx, hypopharynx, and oropharynx to preserve natural speech and swallowing function.

Hoffman et al[1] analyzed 5-year relative survival in cohorts diagnosed with laryngeal cancer in the 1980s and 1990s (1985–1987, 1988–1990,

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1991–1993, 1994–1996) using the NCDB, a national hospital-based cancer registry. Basic demographic data, laryngeal subsite and stage information, and primary treatment were captured. The limitations of such retrospective analyses are many and include the absence of treatment details: the specific drugs, dose, schedule, and timing of chemotherapy; and the type, dose, and timing of radiotherapy, as well as specifics of conservation laryngeal surgery. Such analyses cannot account for treatment selection bias and changes over time in staging definitions and use of imaging. T classification was captured, but N classification was not sufficiently detailed to permit analysis, nor was information provided on neck management, a further limitation. Patient factors that may determine operability and treatment recommendation are missing from retrospective cohort analyses—all of which limit the conclusions that one can draw from such survival trend analyses. However, what specifically was found by these authors to support the notion that preservation of the larynx in patients with locally advanced cancers of the supraglottis and glottis is jeopardizing survival?

Analysis of the NCDB evaluated 5-year survival rates for patient cohorts diagnosed in the 1980s and those diagnosed in the 1990s, uncovering a statistically significant decrease for supraglottic cancer but not for glottic cancer. When analyzed by TNM stage, the decline in survival for supraglottic cancer was largely accounted for by decreased survival of patients with early-stage cancers (T1N0M0 and T2N0M0), a patient group treated with single-modality RT or conservation surgical techniques, and so specified in national treatment guidelines.[7,8] Chemoradiation is not indicated, recommended, or used in clinical practice for stage I and stage II laryngeal cancer. By contrast, the 5-year relative survival rates showed small gains over these time periods for patients with T3N+M0 and T4N0M0 supraglottic cancers (52.1%, 53.4% and 36.7%, 38.4%, respectively, for 1985–1990 and 1994–1995 cohorts).

The authors focus particular attention on T3N0 laryngeal cancer and survival by primary treatment modality. The broad comparison of primary treatment with surgery and treatment without surgery for the 1994 to 1996 cohort showed better 5-year survival for those managed with surgery (64.4% vs 49.4%, $p < .05$). However, analysis specified by treatment modality showed no significant difference in survival among patients treated with chemotherapy + RT (59.3%) or surgery (63.3%) or surgery + RT (65.2%, $p > .05$). Rather, the overall survival difference resulted from significantly worse outcome when primary treatment was RT alone (42.7%), compared with either chemotherapy + RT or surgical management. Does this mean that RT was inferior treatment? Not necessarily, in that selection bias in the treatment of older patients with multiple comorbidities and/or lack of psychosocial supports with RT alone may have occurred—we do not know.

For T3N0M0 glottic cancers, the 5-year relative survival was identical for treatment with chemoradiation or surgery + RT, 65.6%—again, significantly better than treatment with RT alone, 47.9% ($p < .05$). No analysis was provided for T3N0M0 supraglottic cancer but, based on the overall results, one would expect similar findings. Given these outcomes of the NCDB analysis published by Hoffman and colleagues,[1] and the limitations for such retrospective analyses, the implication that the current paradigm of RT with concurrent cisplatin for larynx preservation in lieu of a surgical approach is responsible for the observed survival trends is unsupported.

Another analysis of the NCDB, that of Chen and Halpern,[9] reported survival of patients diagnosed between 1995 and 1998 and found comparable survival outcomes for patients with T3 laryngeal cancer treated with chemotherapy + RT or total laryngectomy, although the survival of T4 patients undergoing total laryngectomy was better than chemotherapy + RT or RT alone. Significant survival differences were also associated with sociodemographic factors of race (black vs white) and health insurance (private vs Medicare, Medicaid, or none), likely reflecting broader socioeconomic factors and increased risk of unchecked comorbid conditions from lack of preventive care. Here again, the impact of selection bias cannot be ascertained from this broad analysis.

Dr. Kerry Olsen, in his thought-provoking commentary, suggests that misuse of concurrent cisplatin + RT in the community is leading to reduced survival among stage III and stage IV patients with laryngeal cancer.[10] He calls for an individualized approach to the treatment for laryngeal cancer that considers tumor pathologic factors, patient wishes, and health-related issues, along with physician expertise and

available facilities. No one would dispute this multidisciplinary practice model, and centers of excellence provide this today. It is noteworthy that in a multivariable analysis, Chen and Halpern[9] found no difference in likelihood of death for patients treated at teaching or research facilities compared with community cancer centers, and only a marginal increase in likelihood for those treated at community hospitals (hazard ratio [HR] for death 1.10, $p = .048$). Furthermore, no survival difference was found when stage III and stage IV patients were analyzed separately, suggesting that laryngeal cancer patients are not being treated differently in the community.

Dr. Olsen gives as indications for total laryngectomy in his practice: (1) failure of RT or RT + chemotherapy, and (2) primary management of T4 cancers that extend through laryngeal cartilage. These recommendations are consistent with data from randomized controlled trials and guideline recommendations. The Veterans Administration (VA) Larynx Cancer Study Group trial compared total laryngectomy and induction cisplatin/5-fluorouracil (5-FU) followed by radiation in responding patients.[4] In all, 56% of T4 patients ultimately required salvage laryngectomy, glottic primaries more frequently than supraglottic, and gross cartilage invasion than no cartilage involvement. Because of these findings and RT alone as one of the treatment arms tested in the Radiation Therapy Oncology Group (RTOG) follow-up intergroup trial (RTOG 91-11), there was consensus among the investigators that tumor penetration *through* cartilage would exclude patients from organ preservation as would extensive cancers of the supraglottis extending deep into the tongue musculature.[5] Thus, only 10% of patients enrolled in RTOG 91-11 had T4 cancers precluding subset analysis. Guidelines specify total laryngectomy for T4 cancers with tumor penetration through cartilage into soft tissue.[7,8]

T3 laryngeal cancers dominated the RTOG 91-11 intergroup trial and thus provided an excellent comparison of 3 nonsurgical approaches to larynx preservation: induction cisplatin/5-FU followed by RT in responders, concurrent cisplatin + RT, and RT alone.[5] Eighty percent of 515 patients had T3 disease, and 50% had N0 (70% N0–1). The results showed similar 5-year survival with all 3 treatments, but statistically significant differences in local control and larynx preservation. These were, respectively, for concomitant treatment compared with induction 71.8% versus 58.4% HR 0.631, $p = .038$ and 83.6% versus 70.5% HR 0.544, $p = .0028$; and for concomitant treatment compared with RT alone 71.8% versus 53.4% HR 0.530, $p = .00031$; 83.6% versus 65.7% HR 0.441, $p = .00016$.[11] Although there was not a surgery control group, the estimated 2-year survival rates for RTOG 91-11 ranged from 74% to 76% for the 3 treatments. This compares favorably with the 68% survival estimate for the surgery control group of the VA trial, keeping in mind the more advanced patients in the latter trial (64% T3, 26% T4).[4,5] These results formed the basis for the current recommendation for concomitant cisplatin + RT as an alternative to laryngectomy.

The option of conservation laryngeal surgery for those T3 cancers with mobile cords is raised by Dr. Olsen. As opposed to T1 and T2 lesions, such management of T3 cancers requires expertise and careful patient selection to be successful. Surgical quality assurance data review revealed that only a very small minority of patients entered into RTOG 91-11 were not candidates for total laryngectomy or, put another way, few would have been candidates for partial laryngeal surgery were the expertise available. The question of whether there may be a difference in treatment effect for fixed cord versus nonfixed cord lesions was explored in an unplanned subset analysis of the RTOG 91-11 trial. This showed a high local failure rate for fixed cord T3 disease treated with induction or RT alone—induction: 49.4% (95% confidence interval [CI] 38.6, 60.3); RT alone: 44.1% (32.8, 55.4), contrasted with treatment with concomitant cisplatin + RT: 28.5% (18.6, 38.4). When cords were not fixed (mobile or impaired), local failure still occurred in nearly half of patients treated with RT alone (49%), whereas the failure rate was the same (29%) with either chemotherapy-containing treatment (unpublished data). These data, although intriguing, are merely hypothesis generating for future trials.

Toxicity from chemoradiation is a concern, although no difference in late effects leading to compromise in swallowing function or chronic aspiration and infection could be detected among treatment groups, and was infrequent in RTOG 91-11. Ability to swallow only liquids was reported in <4% of patients in all groups, and inability to swallow was reported in <3% in all groups. Of the 515 patients treated, only 9 (2 in the chemoradiation group) had laryngectomy performed for laryngeal dysfunction or necrosis.

Thus, the vast majority of patients have an excellent functional outcome, and data to suggest that there is a difference in treatment delivery and functional outcome in the community setting are lacking.

In conclusion, the current treatment paradigm of combined chemotherapy and radiation for T3 and selected T4 laryngeal cancer requiring laryngectomy represents a major advance. The notion that larynx preservation is jeopardizing survival is unsubstantiated and speculative. Of course, the field is not static, and so advances in endoscopic techniques and use of robotics will hopefully change practice patterns, at least at the major referral centers of excellence. The indications for such treatments beyond early-stage T1 and T2 disease, however, should derive from randomized controlled trials and not just institutional case series, as has been the historical development of surgery in head and neck cancer. For T3 and T4 disease, systemic therapy will continue to be part of multidisciplinary treatment, but refined by the identification of molecular predictive and prognostic factors that allow risk stratification and more rational treatment selection. The latter is what will allow the leap to be made in survival of patients with laryngeal cancer that we all seek.

REFERENCES

1. Hoffman HT, Porter K, Karnell LH, et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. Laryngoscope 2006;116 (Suppl 111):1–13.
2. Lefebvre JL, Rolland F, Tesselaar M, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. J Natl Cancer Inst 2008;101:142–152.
3. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890–899.
4. Wolf GT, Hong WK, Gross Fisher S, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer (The Department of Veterans Affairs [VA] Laryngeal Cancer Study Group). N Engl J Med 1991;324:1685–1690.
5. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349: 2091–2098.
6. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009;101:498–506.
7. Forastiere AA, Ang KK, Brizel D, et al. Head and neck cancers. J Natl Compr Canc Netw 2008;6:646–695.
8. Pfister DG, Laurie SA, Weinstein GS, et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. J Clin Oncol 2006;24:3693–3704.
9. Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 2007;133:1270–1276.
10. Olsen K. Reexamining the treatment of advanced laryngeal cancer. Head Neck 2009;31:000–000.
11. Forastiere AA, Maor M, Weber R, et al. Long-term results of intergroup RTOG 91-11: a phase III trial to preserve the larynx—induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy. Proc Am Soc Clin Oncol 2006;24:284s (abstract).