ORIGINAL ARTICLE

Cost Comparison of Surgery vs Organ Preservation for Laryngeal Cancer

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Objective: To perform a cost minimization analysis of total laryngectomy with postoperative radiotherapy vs induction chemotherapy with subsequent radiotherapy in patients with advanced (stage III or IV) squamous cell carcinoma of the larynx.

Design: Decision-analysis model using data from peer-reviewed trials, case series, meta-analyses, and Medicare diagnosis related group reimbursement rates.

Setting and Patients: A hypothetical cohort of patients with stage III or IV laryngeal cancer. The perspective is that of a health care payer.

Interventions: The hypothetical patient cohort could receive (1) surgery (total laryngectomy) with postoperative radiotherapy or (2) induction chemotherapy (fluorouracil and cisplatin) with radiotherapy followed by salvage surgery for patients failing to respond to chemotherapy.

Main Outcome Measure: Overall difference in direct medical costs in 2003 US dollars between the 2 treatment arms from initiation to completion of treatment.

Results: In the baseline analysis, the direct medical costs for the surgical arm were $30 138 per patient. For the organ preservation arm, the direct medical costs were $33 052 per patient. The finding that the surgical arm costs were lower was robust to all sensitivity analyses except for the extreme low estimate for the cost of chemotherapy.

Conclusions: Our results suggest that total laryngectomy with postoperative radiotherapy costs nearly $3000 less than organ preservation treatment for advanced laryngeal cancer. Given that survival appears equivalent between the 2 modalities, cost consideration and patient preference may be important factors in decision making for the treatment of advanced laryngeal cancer.

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TRADITIONAL THERAPY FOR advanced (stage III or IV) laryngeal cancer long included total laryngectomy followed by postoperative radiotherapy. During the past decade, organ preservation protocols have been introduced in an effort to preserve the larynx. These treatments have generally consisted of combinations of chemotherapy and radiotherapy, with total laryngectomy reserved for patients who do not respond to treatment.

A large randomized controlled trial by the Department of Veterans Affairs Laryngeal Cancer Study Group[1] prospectively compared survival between the traditional surgical protocol vs an organ preservation protocol. This study showed no significant difference in 2- or 5-year survival between the 2 treatment arms and higher rates of larynx preservation in the organ preservation arm. Although some studies[2,3] suggest that organ preservation leads to better overall quality of life, others[4-6] have failed to detect significant differences in global quality of life between the 2 treatment protocols.

Given the similar survival rates and questionable quality-of-life differences between surgical and organ preservation protocols in advanced laryngeal cancer, the costs of therapy may offer additional insight into decision making. Few economic evaluations have been published for advanced laryngeal cancer, particularly in the United States.[7] The objective of this study was to perform a cost minimization analysis comparing total laryngectomy and postoperative radiotherapy vs organ preservation in the treatment of advanced laryngeal cancer. We applied a cost minimization strategy, as this technique is used to choose a technology when outcomes are equivalent.[8]

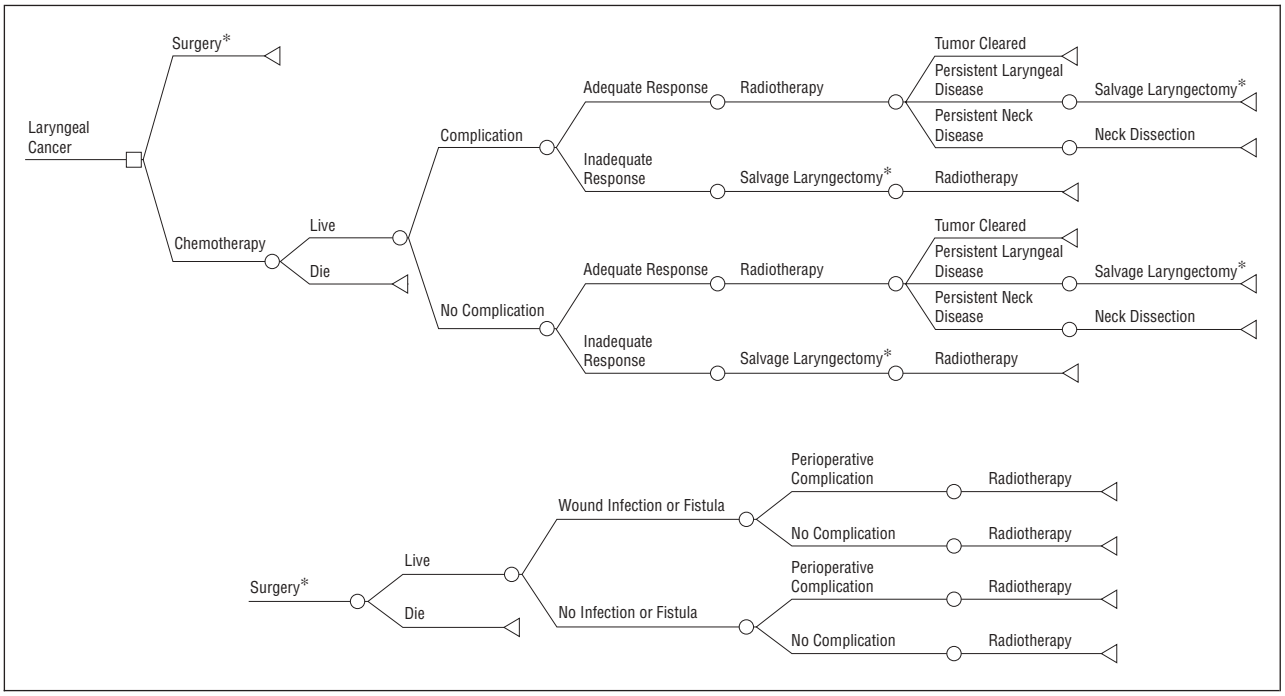

Figure 1. Decision analysis tree. A square signifies a choice; circle, a probability; and a triangle, a "terminal node" or the end point. Asterisks denote linking the upper "laryngeal cancer" tree to the lower "surgery" tree.

METHODS

MODEL

We constructed a decision model to track treatment probabilities and direct medical costs in a hypothetical cohort of 1000 patients with advanced (stage III or IV) laryngeal cancer (**Figure 1**). The time horizon for the analysis covered the period from initiation through completion of treatment (approximately 20 weeks). This model did not include longer-term outcomes, such as tumor recurrence, as these rates are similar between the 2 treatment arms.[1] Costs included direct medical costs for surgery or induction chemotherapy, both followed by radiotherapy, as well as subsequent salvage surgery for failure to respond to chemotherapy. The perspective of the model was that of a health care payer.

In our model, patients with advanced laryngeal cancer were treated with laryngectomy plus postoperative radiotherapy or with an organ preservation protocol consisting of induction chemotherapy followed by radiotherapy and, when necessary, surgery for salvage (Department of Veterans Affairs Laryngeal Cancer Study Group[1] protocol).

Surgical Arm

In this model, patients in the surgical arm undergo total laryngectomy with regional neck dissection followed by postoperative standard fractionation external beam radiotherapy. Patients are subject to surgical mortality, postoperative wound complications (including infection and fistula formation), and respiratory and cardiac complications. There are 5 potential end points ("terminal nodes") for these patients (Figure 1).

Organ Preservation Arm

In the organ preservation arm, patients undergo 2 cycles of induction chemotherapy followed by examination under anesthesia to assess tumor response. Poor responders undergo salvage laryngectomy and are subject to the same complications as described in the surgical arm, although the risks for each outcome may differ. Patients with adequate response to chemotherapy undergo a third cycle of chemotherapy and then radiotherapy. We assume 3 potential outcomes in these patients: (1) tumor clearance, (2) persistent laryngeal disease requiring salvage laryngectomy, or (3) persistent or new neck disease requiring a neck dissection. Patients requiring salvage laryngectomy or neck dissection are then at risk for the same surgical complications as previously described. Therefore, the organ preservation protocol has 27 possible end points (terminal nodes) (Figure 1).

LIKELIHOOD OF EVENTS

The probabilities of clinical events used in the decision model are shown in the **Table**. We defined baseline value as the reference value used in our primary analysis. The baseline value represents the mean value when more than 1 value was found in the literature or represents the mean value when a specified range was reported in a published report.[28] The range specified for each baseline value in the table reflects the range reported in a published study, or if a range was not given, the range was created by adding or subtracting 20% from the base-case value.[29] The inclusion of a range is important to create best- and worst-case scenarios in the sensitivity analyses.

MORTALITY AND RESPONSE RATES TO TREATMENT

Operative mortality was estimated from the Department of Veterans Affairs Laryngeal Cancer Study to be 2%.[1] There was no published mortality range to use for the sensitivity analysis; therefore, we defined a best-case scenario with a mortality of 1% and a worst-case scenario with a mortality of 8%, based on anecdotal experience. We estimated mortality from chemotherapy to be 3% from the Department of Veterans Affairs Laryngeal

Table. Variables Used in the Decision Analysis Model

Variable	Baseline Value (Range)	Source
	Rate, %	
Mortality of total laryngectomy	2 (1-8)	Department of Veterans Affairs Laryngeal Cancer Study Group,[1] 1991
Mortality of chemotherapy	3 (1-5)	Department of Veterans Affairs Laryngeal Cancer Study Group,[1] 1991
Wound infection or fistula without prior radiotherapy	13 (10-16)	Shemen and Spiro,[9] 1986 Redaelli de Zinis et al,[10] 1999
Wound infection or fistula with prior radiotherapy	30 (23-37)	Weber et al,[11] 2003 Shemen and Spiro,[9] 1986 Leon et al,[12] 2001 Sassler et al,[13] 1995
Chemotherapy complication	8 (3-13)	Caponigro et al,[14] 1999
Perioperative complication without prior radiotherapy	21 (7-43)	Shemen and Spiro,[9] 1986 Mathew et al,[15] 1999 Fogarty et al,[16] 1999
Perioperative complication with prior radiotherapy	22 (7-45)	Goodwin,[17] 2000 Weber et al,[11] 2003 Shemen and Spiro,[9] 1986 Mathew et al,[15] 1999 Fogarty et al,[16] 1999
Adequate response to chemotherapy	82 (74-90)	Department of Veterans Affairs Laryngeal Cancer Study Group,[1] 1991
Tumor clearance from chemotherapy	70 (60-80)	Department of Veterans Affairs Laryngeal Cancer Study Group,[1] 1991 Weber et al,[11] 2003
	Cost, 2003 US $	
Total laryngectomy	17520 (13500-20000)	Myers et al,[18] 1994 Arnold et al,[19] 2000 Yueh et al,[20] 2003 Gates et al,[21] 1982
Chemotherapy	15567 (10500-20500)	Laramore,[22] 1995 Vokes et al,[23] 1989
Radiotherapy	8505 (7000-10000)	Myers et al,[18] 1994 Arnold et al,[19] 2000 Bailey et al,[24] 1990
Chemotherapy complication	5478 (3500-7500)	Rosenman et al,[25] 2002
Neck dissection	7479 (5500-9500)	Chen et al,[26] 2000
Wound complication or fistula	24915 (12000-38000)	Yueh et al,[20] 2003
Perioperative complication	5306 (2700-8200)	Centers for Medicare & Medicaid Services,[27] 2000

Cancer Study. Mortality from salvage laryngectomy was obtained from a meta-analysis[17] of 7 published studies that reported a mean rate of 5%.

Chemotherapy response rates were estimated from the Department of Veterans Affairs Laryngeal Cancer Study, in which 82% of patients showed an adequate tumor response.[1] From the same study and data from the Radiation Therapy Oncology Group trial 91-11 by Weber and colleagues,[11] 70% of patients had complete clearance of their tumor, 22% had persistent primary laryngeal disease, and 8% had persistent neck disease. We used these probabilities for the baseline analysis.

COMPLICATION RATES IN NONCHEMOTHERAPY AND NONIRRADIATED PATIENTS

The rate of fistula formation in nonirradiated patients without a history of chemotherapy use ranged from 10% in a study[9] of 100 consecutive laryngectomy patients to 16% in another study[10] that reviewed medical records from 246 patients. We used the mean rate of 13% as the baseline value for this model. We compiled rates of perioperative respiratory and cardiac complications from 4 studies, which reported these complications in a mean of 21% of cases. Of these studies, one[15] determined the rate of respiratory complications to be 14% in general surgery patients, another[9] showed a 25% incidence of pneumonia in laryngectomy patients, and the third study[16] showed that 43% and 13% of patients develop respiratory and cardiac complications, respectively, among patients who have undergone head and neck reconstruction. The rates of complications from radiotherapy are similar in the 2 treatment arms and therefore were not modeled.[1]

COMPLICATION RATES IN CHEMOTHERAPY AND IRRADIATED PATIENTS

Patients who have had prior chemotherapy and radiotherapy may exhibit higher rates of perioperative complications, surgical complications, and mortality. Based on a phase 2 trial by Caponigro and colleagues[14] that used a similar chemotherapy regimen, febrile neutropenia was the most common serious complication requiring hospitalization and occurred in 8% of patients. Furthermore, in this postchemotherapy and postradiotherapy population, wound complication and fistula formation incidences were on average 30% from 4 studies.[9,11-13] The incidence of postoperative complications (ie, cardiac and respiratory complications) in these postchemotherapy and postradiotherapy patients was approximately 22% based on 5 studies.[9,11,15-17] Last, patients with persistent neck disease who required a neck dissection had similar rates of respiratory and cardiac complications but experienced lower rates of wound complications compared with laryngectomy patients.[30]

COSTS

Direct medical costs were obtained from different sources, including published peer-reviewed studies and Medicare reim-

bursement rates for diagnosis related groups (Table). Costs and amounts reimbursed were used rather than charges to allow accurate comparisons of actual expenses between institutions.[31] When charges were given in a study, we converted them to costs by applying institution-specific cost-to-charge ratios for the study site.[32] When more than 1 study identified a cost for a variable in the model, a mean value was used. All costs were adjusted for inflation to 2003 US dollars based on the Consumer Price Index (US Department of Labor). Discounting was not applied to this analysis because events in the model occur within 1 year.

Costs for laryngectomy averaged $17 520 from 3 peer-reviewed sources.[18-20] Cost data were not published in 1 report,[20] but the raw data were available for cost calculations. In addition, we included the cost of voice rehabilitation ($333) estimated from a report of 103 laryngectomy patients.[21]

Cost data for wound infection and fistula formation were obtained from a study[20] evaluating the effect of critical pathways in the treatment of laryngeal cancer. Although the methods of patient identification and medical chart abstraction were described previously,[20] the cost data have not been previously reported, to our knowledge. In brief, an inception cohort of laryngectomy patients at Yale–New Haven Hospital, New Haven, Conn, was assembled using the hospital's financial database to identify patients with *International Classification of Diseases, Ninth Revision,* procedure codes of 30.3 (complete laryngectomy) or 30.4 (radical laryngectomy) from September 1, 1992, through February 28, 1999. Medical records were reviewed to eliminate patients who underwent total laryngoesophagectomy, total laryngopharyngectomy, total glossolaryngectomy, and partial laryngectomy. In addition, the medical records were used to document the clinical course after laryngectomy, including all relevant medical and surgical complications. The financial database, which used cost-based accounting methods to report true costs of care, was then accessed to provide the costs associated with each hospitalization.

We identified the costs incurred by the hospital based on 87 consecutive patients with laryngeal cancer who underwent laryngectomy. Six patients (7%) developed a fistula, infection, or wound dehiscence, which is consistent with prior reports on complication rates after laryngectomy.[9,10] On average, patients who developed wound complications incurred a mean of $24 915 more costs than patients without wound complications.

Costs for perioperative medical complications, including respiratory and cardiac complications, were estimated using the Centers for Medicare & Medicaid Services 1999 *Diagnostic Related Group Manual*[27] reimbursement rates, as no adequate published data were available. The mean cost of these complications was $5307.

Costs related to radiotherapy ($8505) were extracted from 3 published sources and averaged. These studies included a retrospective review of 57 patients with laryngeal cancer from Iowa,[19] the billing records of a patient from Texas,[24] and a retrospective review of 50 patients from Pittsburgh, Pa.[18]

To account for costs related to chemotherapy, the data from 2 published reports were averaged, amounting to $15 567 for 3 cycles (reference case value) and $11 296 when only 2 cycles were delivered.[22,23] One of these studies[23] was a randomized trial comparing inpatient vs outpatient chemotherapy. The other report[22] was an editorial survey of laryngeal cancer patients. The costs assigned to chemotherapy also included the cost of an examination under anesthesia to determine tumor response to chemotherapy and were estimated from the editorial survey to be $2754.[22] The range used in the sensitivity analysis for the cost of chemotherapy was $10 500 to $20 500. Chemotherapy complication costs ($5478) were obtained from a retrospective review of 157 pediatric cancer patients with febrile neutropenia.[25] All surgical costs for patients who failed to respond to chemotherapy were previously described in the surgical arm, except for the cost for neck dissection in patients with residual or progressive neck disease. This estimate ($7479) was derived from a single cross-sectional study[26] evaluating clinical pathways in head and neck oncology.

SENSITIVITY ANALYSIS

We performed a series of 1-way sensitivity analyses on all variables in the model to evaluate the uncertainty in our analysis. These analyses were performed by varying one variable at a time while holding the others fixed.[29] The ranges of probabilities and costs examined in the sensitivity analyses reflect the ranges reported in the Table.

RESULTS

For the base-case analysis, initial surgical management resulted in an expected cost savings of $2914 per patient in direct medical costs compared with management with an organ preservation protocol. The expected costs for a patient who underwent surgical resection of the larynx followed by postoperative radiotherapy totaled $30 138. The estimated costs calculated for a patient in the organ preservation arm totaled $33 052.

Patients who failed induction chemotherapy and underwent salvage laryngectomy, developed a wound infection or fistula, and had a perioperative complication incurred the greatest costs, at $77 291 per patient. The patients acquiring the least costs were those who died following induction chemotherapy ($15 568 per patient).

The effect of the individual variables on the cost difference is shown in a series of 1-way sensitivity analyses in **Figure 2**. This figure represents the uncertainty in our analysis. In the figure, the vertical line at zero represents values at which there is no difference in cost between surgery and organ preservation strategies. The vertical line at "Baseline Values" represents the resultant cost savings ($2914 per patient) of surgery over organ preservation when applying the baseline values used in our primary analysis (see the "Likelihood of Events" subsection in the "Methods" section). The figure shows that surgery remained the dominant (cheapest) strategy in nearly all of the sensitivity analyses. Variation in mortality rates, wound infection rates, chemotherapy complication rates, response rates to chemoradiotherapy, cost of laryngectomy, cost of radiotherapy, and cost of wound complications did not alter the finding that surgery was less expensive than organ preservation. The only scenario in which surgery was more expensive was when we used the low range ($10 500 per patient) of our estimates for the cost of chemotherapy. We found that the cost of chemotherapy also yielded the greatest variation in the results, producing overall cost differences ranging from $2154 cost savings for chemotherapy to $7846 cost savings for surgery. Most important, varying the cost of laryngectomy even to the most expensive value ($20 000 per patient) did not favor organ preservation.

COMMENT

According to the decision-analysis model in this study, total laryngectomy with postoperative radiotherapy yields lower direct medical costs by $2914 per patient com-

pared with an organ preservation protocol in the management of advanced laryngeal cancer. This finding agrees with that reported by Leon and colleagues,[33] who retrospectively reviewed medical records from 96 patients from Spain with stage III glottic tumors and found surgery to be less expensive than organ preservation by €600.

The results from our model were consistent in all but 1 of the 14 sensitivity analyses, which suggests that our findings are robust. Only when the cost of chemotherapy was at the least expensive extreme was organ preservation less expensive than initial surgical management. However, the study[23] we used to provide the low estimate for the cost of chemotherapy was derived using mean hospital bed costs and pharmacy charges, not individual-specific billing or cost records. This study likely underestimates the cost of chemotherapy because it did not account for additional costs, including nonchemotherapy medications (such as antinausea medications), laboratory work, or physician fees. Had this study been excluded from the model, our results would be robust to all sensitivity analyses.

It is important to recognize several limitations. We modeled only the initial phase of treatment and did not account for late tumor recurrence or costs associated with late tumor recurrence or surveillance. This decision was based on the approximate equivalence of tumor recurrence between the 2 treatment protocols reported, at 25% in the surgery protocol and 31% in the chemotherapy protocol.[1] In addition, long-term data are not available to project these rates beyond 5 years. Therefore, long-term differences in outcome may not be accounted for.

A few key indirect medical costs were included in the model, such as the cost of voice rehabilitation. Other indirect medical costs, such as caregiver expenses, were not included, because these are not expenses from the perspective of the health care payer. Similarly, indirect nonmedical costs, including productivity loss and travel expenses, were not modeled. Inclusion of indirect costs would likely further favor surgery in the model, as the duration of indirect medical care needs, including home care assistance, associated with 3 cycles of chemotherapy is longer than that routinely required for surgery.

Finally, the results of this study are based on a hypothetical model and cost estimates taken from diverse sources. Actual organ preservation protocols may vary somewhat from this model. This is an inherent limitation of the rigidity of the decision-analysis method.[34,35] However, this technique permits valuable insight into not only estimates for cost differences but also the factors that most strongly affect overall comparisons between costs of treatment (cost of chemotherapy and cost of laryngectomy). Prospective analyses with directly measured costs are needed to confirm these results.

CONCLUSIONS

This cost minimization study is the first attempt to quantify the costs related to 2 treatment modalities for advanced laryngeal cancer in the United States, to our knowledge. Our results suggest that there is a cost savings of approximately $2914 per patient between initial surgical management plus postoperative radiotherapy ($30 138) and an organ preservation protocol ($33 052). Given that survival is equivalent between the 3 modalities, cost considerations may also play an important role in decision making about selecting treatment for advanced laryngeal cancer.

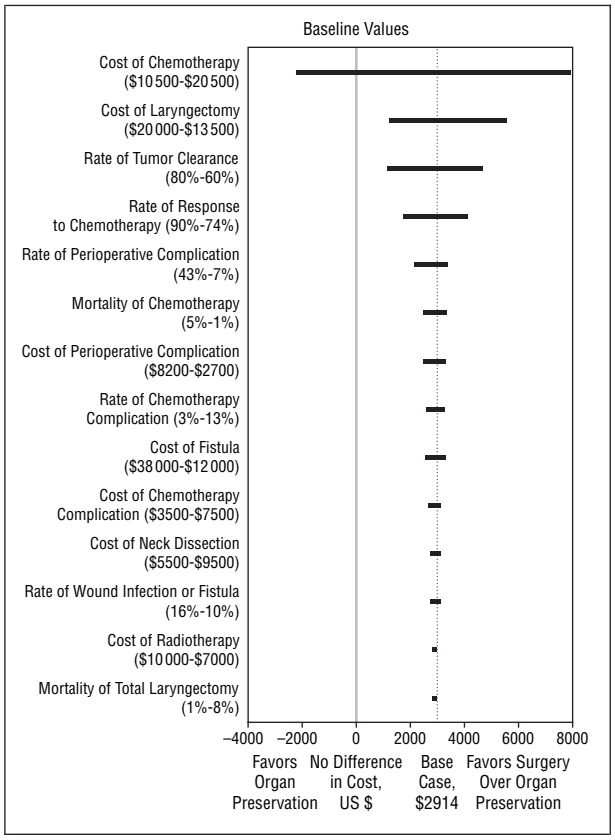

Figure 2. One-way sensitivity analyses for incremental costs: the effect of varying individual variables illustrates consistent cost savings of initial surgical management over organ preservation. For ranges, the first value represents the result on the left side of the corresponding horizontal bar, whereas the second value represents the result on the right side of the horizontal bar.

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