THE TREATMENT OF EARLY LARYNGEAL CANCERS (T1–T2 N0): SURGERY OR IRRADIATION?

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Abstract: Background. Carcinoma of the larynx is the most common cancer affecting the head and neck region. In Northern Europe, early laryngeal cancer is almost universally treated by irradiation, but elsewhere it is treated by surgery. The main aim of this study was to determine whether there was any difference in survival between the two main therapeutic options. The secondary aim was to assess speech and voice quality in a small, randomized sample of patients from each treatment group.

Methods. The subjects investigated were 488 patients with T1–2, N0 squamous cell carcinoma of the larynx. The patients form an unselected sequential group of our institution’s experience with treating this disease over three decades. Four hundred nineteen patients were treated by irradiation, and 69 were treated with surgery. Most surgical patients were treated earlier in the series, whereas radiotherapy later became the treatment of choice. The primary outcome measures were recurrence at the primary site, recurrence in the neck, and tumor-specific survival. The secondary outcome measure was speech and voice quality. Statistical analysis was by univariate and multivariate analysis of association and survival. Surgery included horizontal or vertical partial laryngectomy and various minor procedures on the glottis, including cordectomy. Over a 30-year period, radiotherapy was administered to a dose of 60–66 Gy given over 30–33 daily fractions.

Results. Surgery tended to be performed early on in the series and radiotherapy thereafter. Surgery was more likely to be carried out for supraglottic disease. These differences apart, the radiotherapy and surgery groups of patients were well matched. The 5-year tumor-specific survival for those treated by irradiation was 87% and for surgery it was 77% (p = .1022). Glottic cancer and T1 disease were associated with high 5-year survivals: 90% and 91%, respectively. Supraglottic site and T2 disease both had a poorer prognosis: 79% and 69%, respectively. The differences for both sets of data were significant. There was no significant difference in primary site recurrence rates for the two treatment modalities, but regional recurrence was higher in the surgery group. Further analysis demonstrated that this was not a function of surgery per se but rather of the unit’s policy toward the N0 neck at the time surgery was carried out. Regarding speech and voice quality, radiotherapy was far superior to surgery. All patients in the radiotherapy group but only 3 of 10 in the surgery group were judged to have a good or normal voice (p = .0017).

Conclusions. Both surgery and irradiation are equally effective at treating early laryngeal carcinoma. Speech and voice quality were highly significantly better in patients treated by irradiation than in those treated by surgery. © 2004 Wiley Periodicals, Inc. Head Neck 26: 127–135, 2004

Keywords: partial laryngectomy; conservative laryngectomy; speech and voice quality; head and neck cancer; squamous cell carcinoma

Cancer of the larynx is the most common cancer of the head and neck, excluding the skin.1 Treatment of early laryngeal cancer remains controversial, largely because of the dearth of prospective randomized trials. It would seem that early laryngeal cancer could be treated with equal success by either radiotherapy or by conservative surgery.2–8
The preferred treatment modality at present is highly dependent on geography, with radiotherapy tending to be the treatment of choice in northern Europe, whereas patients are more likely to be treated with surgery in the United States and southern Europe.

Over the past one and a half decades, our institution has adopted an organ preservation strategy favoring primary radical radiotherapy followed, if necessary, by salvage surgery. This strategy evolved over the years is based on the premise that treatment goals should include cure with acceptable side effects, minimal complications, and laryngeal preservation. Irradiation treatment failures can usually be salvaged by total or partial laryngectomy. The data for this article have been collected in a prospective manner over a period of 30 years and include the first decade when surgery rather than radiotherapy was the treatment of choice for these cancers. During the last two decades, radiotherapy gradually superseded surgery as the treatment of choice, and thus we are able to compare the results of surgery with radiotherapy for the treatment of early laryngeal cancer.

The aim of this article is therefore to compare the results of the two treatment modalities in terms of recurrence at the site of the primary tumor, in the neck, and survival. Associations between variables were also studied. A small, intercalated study investigates speech and voice quality in patients from each treatment modality.

**METHODS**

**Methodology and Analysis of Electronic Data.** The department of Head and Neck Surgery at the University of Liverpool has recorded details on all patients treated since 1963 in a prospective manner on a pro forma basis. Twenty-five years ago these data were converted to an electronic database, and the details of each patient’s tumor, treatment, and follow-up were maintained. The present data include 488 patients with T1 or T2 squamous cell carcinoma of the larynx with no regional or distant metastatic disease. In the first group, 419 patients were treated with primary irradiation with curative intent. In the second group, 69 patients were treated with primary surgery with curative intent (Table 1).

In the radiotherapy group, supravoltage radiation was administered by a 5 or 6 MeV linear accelerator. The dose ranged from 60–66 Gy given over 30–33 daily fractions. Patients were immobilized in a beam-directing plastic shell and treated with anterior oblique double-wedged fields.

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<th>Table 1. Host and tumor factors.</th>
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<td><strong>Host</strong></td>
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<td>Age (mean y)</td>
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Of the 69 patients in the surgical group, 28 were treated by (horizontal) supraglottic laryngectomy, 16 by vertical hemilaryngectomy, 12 by endoscopic laser surgery, and 13 by microlaryngoscopic surgery. Two patients received postoperative radiotherapy.

In the database, the stage of the tumor at presentation (and recurrence) was classified using the current UICC and AJC classification. Because these classifications were subsequently modified, the data fields were updated to the most recent UICC and AJC classification. The general condition of the patient was recorded with the method recommended by the Eastern Co-operative Oncology Group. The histologic grade was assigned to well, moderately, or poorly differentiated squamous cell carcinoma. The database also details the date and cause of death, follow-up times, and times and details of any recurrence. Data on follow-up were collected from clinic visits, general practitioner records, The Merseyside and Cheshire Cancer Registry, and the Statistics Office. Three patients in the radiotherapy group were lost to follow-up.

Data were entered sequentially, as each patient was dealt with in the head and neck clinic. In this study, there was no selection applied, and all patients entering the clinic were included in the study. Two patients lost to follow-up were included, and both had in excess of 5 years follow-up. There were five exceptions. One patient was lost to follow-up after only 6 months, and four patients were excluded because of incomplete data fields.

The median potential follow-up was 16.6 years. For data analysis, data were transferred from the database to the SAS statistical package on a Pentium Microcomputer (Statistical Analysis Systems Version 8.2 SAS Institute, Cary, NC). Various host and tumor factors were included in the analysis (Table 1), as well as follow-up data including details of any recurrence.

Differences between the two treatment groups were displayed on contingency tables and analyzed by chi-square (Table 1). The data were further analyzed using the multivariate method of multiple logistic regression (the CATMOD procedure). As with other classes of multiple regression, a model was constructed containing the variables of interest, which included the host and tumor factors detailed in Table 1, as well as the type of treatment and follow-up data. Initially, the model was inclusive but was progressively refined by forward and backward elimination. This was carried out manually initially and then automatically using the SAS STEPWISE procedure. The model was reconstructed several times in the search for associations between variables.

Survival curves were constructed using the method of Kaplan and Meier (the LIFETEST procedure in the SAS software). Differences in survival curves were analyzed using the log rank test. Actuarial development of recurrence was also calculated using the Kaplan–Meier method. Confidence intervals for the surviving or recurring proportions were calculated by the method of Greenwood. Further analysis of survival was carried out using Cox’s proportional hazards model (the LIFEREG procedure) using the same parameters and method as for multiple logistic regression.

**Intercalated Study of Voice Quality.** Although it must be emphasized that such an assessment was not the primary aim of this article, it was believed to be appropriate to carry out a small, randomized study comparing the voice quality of patients from the two treatment groups.

A program was written in BASIC to extract randomly 10 patients from each treatment group (who were still alive). Five patients in the radiotherapy group and three in the surgery group still attended the outpatient clinic. The other patients were contacted by telephone and letter. Two patients in the radiotherapy group and one in the surgery group did not wish to be studied. These patients were replaced randomly as previously. The median time since treatment for the surgery group was 9.6 years, and for the radiotherapy group it was 8.5 years. The patients in the surgery group were older (mean age, 75 years) than those in the radiotherapy group (mean age, 65 years) (Fisher’s exact test; \( p = .0481 \)). There were no other significant differences between the two groups.

Voice and speech quality was assessed by a simple scoring system validated in our department and against other standard questionnaires. The scoring method was a simple 4-point score with no central value:

1. Normal voice and speech.
2. Good voice and speech.
3. Moderate voice and speech.
4. Poor voice and speech.

All test patients read three standard paragraphs recorded by a digital tape recorder in a sound-proofed room. A panel of five listeners assessed recordings. This panel was composed of a
speech pathologist, two head and neck surgical oncologists, a senior nurse, and a lay individual.

Data from this small intercalated, but randomized, study were analyzed by Fisher's exact test.

RESULTS
The host and tumor factors for both treatment groups are shown in Table 1. The mean age of the radiotherapy group was 63 years, and the mean age for the surgical group was 61 years. There was no significant difference in male–female ratio for the two groups. Seventy-three percent of the patients in the radiotherapy group were in good physical condition, and 75% of the patients in the surgery group were also physically fit (ECOG 0). Most of the remaining patients were reasonably well (ECOG 1) in both groups. There was no significant difference in the ECOG rating between the two groups. As regards histologic findings, nearly all patients had well or moderately differentiated squamous cell carcinoma, and there was no significant difference in the pathologic grading between the two groups. Seventy-five percent of patients in the radiotherapy group were staged T1 and the same proportion in the surgery group. When the site between the two groups was studied, significant differences were found. Twenty-two percent of the radiotherapy group had supraglottic cancer compared with 50% in the surgery group. Seventy-six percent of patients in the radiotherapy group had glottic cancer and 35% in the surgery group. Eight patients in the radiotherapy group had subglottic cancer, and four patients had this disease in the surgery group. The difference was highly significant \( p < .0001 \).

Categorical data were analyzed by chi-square or Fisher's exact test and then by categorical modeling. Radiotherapy was more likely to be given for glottic cancer, and surgery was more likely done for supraglottic cancer (estimate \( = 0.8191; p < .0001 \)). Year of treatment was also included in the model, and it was found that patients tended to have surgery in the 60s and 70s, whereas in the 80s and 90s patients tended to have irradiation (estimate \( = 1.5430; p < .0001 \)).

No significant difference was found when recurrence at the primary site for those patients treated by surgery or by irradiation was studied. At 5 years, 20% of the irradiation group (95% confidence intervals, 18%–22%) had a primary site recurrence compared with 22% in the surgery group (95% confidence intervals, 19%–25%) \( (p = .7205) \). At 10 years, the respective figures were 22% and 23% (Figure 1).

There was a significant difference in the pattern of recurrence (or strictly speaking, occurrence) in the neck between the two treatment groups (Figure 2). Only 9% of those who were treated with irradiation had a recurrence in the neck (95% confidence intervals, 8%–10%). Twenty-five percent of patients in the surgery group had a recurrence in the neck (95% confidence intervals, 8%–10%).
recurrence in the neck (95% confidence intervals, 21%–28%); this difference was highly significant ($p < .0001$). The respective 10-year figures were 10% and 25% (Figure 2). Neck recurrence was significantly more likely to develop in supraglottic cancer compared with glottic cancer (20% and 12%, respectively, $p < .0001$). Regional recurrence was also more common in T2 disease than T1 disease (19% and 10% respectively, $p < .0001$).

The actuarial cause-specific survival at 5 years for those patients treated with irradiation was 87% (95% confidence intervals, 83%–99%) and for those having surgery 77% (95% confidence intervals, 65%–89%). The difference was not significant ($p = .1022$). At 10 years, the survival figures were 84% and 77% (Figure 3).

Stratification analysis of survival was carried out for primary treatment modality, site, and
stage. The combined plots for treatment and site are shown in Figure 4 and demonstrate a difference in survival between glottic and supraglottic tumors. There was no difference in survival for treatment modalities, but a significant ($p = .0166$) difference was found in survival for site. Glottic cancer was associated with a 90% 5-year survival (95% confidence intervals, 88%–92%) and no reduction at 10 years. For supraglottic cancer, the 5-year survival was 79% (95% confidence intervals, 73%–85%) and for the 10-year survival was 74%.

T stage was similarly analyzed (Figure 5) and demonstrated no difference for treatment moda-
lity regarding stage but a significant difference between T1 and T2 disease \( (p < .0001) \). Those patients with T1 disease had a 91% 5-year survival (95% confidence intervals, 89%–93%) and a 10-year survival of 90%. Those with T2 tumors had a 69% 5-year survival (95% confidence intervals, 61%–77%) and a 10-year survival of 67%.

The data were analyzed further by Cox’s proportional hazards model. Age, gender, site, histologic findings, T stage, pathologic T stage, performance data (ECOG), treatment, year of treatment, recurrence at the primary site, and recurrence in the neck were all included in the model. After forward and backward elimination, it was confirmed that supraglottic disease was associated with a relatively poor prognosis compared with glottic cancer (estimate, 0.7945, \( p = .0331 \)) and that the greater the T stage the worse the survival (estimate, 1.7758, \( p < .0001 \)). In addition, recurrence at the primary site was associated with a poor prognosis (estimate, 1.5325, \( p = .0001 \)) as was recurrence in the neck (estimate, 2.47604, \( p = .0001 \)). Both the treatment modality and the year of treatment were not significantly related to survival (estimate, 0.4534) (estimate, 0.0137).

**Complications.** In the radiotherapy group, two patients had moderate dysphagia requiring liquid food and two had mild dysphagia but could take an essentially normal diet. These problems were due to delayed postirradiation fibrosis. Another patient had cartilage necrosis that eventually settled on a regimen of oral tetracycline and steroids.

In the surgery group, four patients had a fistula, and all but one of these healed spontaneously: one patient required a flap repair. Two had moderate stenosis requiring dilatation, and four had serious medical problems; one of whom died.

**Voice and Speech Quality.** Ten patients from each treatment group were recruited randomly. In the radiotherapy group, eight were scored as normal and two as good. For the surgery group, three patients had good voice and speech, four had moderate voice and speech, and three had poor voice and speech. This difference was highly significant (Fisher’s exact test, \( p = .0017 \)).

**DISCUSSION**

The results of this study demonstrate that both radiotherapy and surgery are equally successful at curing early laryngeal cancer as assessed by univariate and multivariate analysis. It is important to consider two points when assessing the data. First, patients with supraglottic cancer were more likely to be treated by surgery. This is a high-risk group both for occult node disease and regional recurrence (“occurrence”). In this series, it was not the policy of our institution to treat occult node disease; rather the “wait and watch policy” was adopted.

Second, radiotherapy tended to be given later in the series and for glottic cancer. Glottic cancer is not usually associated with occult nodes, but radiotherapy (in this series) included the first echelon nodes, particularly in supraglottic cancer.

Although small, the random sample of 20 patients assessed for speech and voice quality demonstrate, very clearly, the superiority of radiotherapy in preserving this crucial part of laryngeal function.

Both surgery and radiotherapy as treatment for early laryngeal cancer have their champions, and much has been published in the literature describing the results of both modalities at various institutions.\textsuperscript{15–25} Part of the reason that the optimal treatment remains controversial is the absence of a definitive prospective comparative analysis of treatment options. This remains elusive partly because of difficulties in defining “early,” resulting in some authors including carcinoma in situ in their series,\textsuperscript{20,26} which would produce a more favorable outcome, compared with series only including invasive carcinomas. Difficulties also arise because of the imperfections in the staging system. Clinical staging may not correlate with pathologic staging, resulting in T4 carcinomas of the glottis being included as T1 when pathologic evaluation is not available to show microscopic invasion of adjacent cartilage or extralaryngeal soft tissues.\textsuperscript{27} This understaging is obviously a possibility with radiotherapy when only clinical staging is available. Although not a prospective study, this article evaluates data collected in a prospective manner with no attempt at selection, and we can infer some degree of standardization, because all the patients have been treated at one institution, and only two clinicians have entered data into the database.

Our results do not show any significant difference in recurrence at the primary site or in actuarial cause-specific survival between the two groups. It does show, however, a significant difference in neck recurrence, with a higher proportion of patients treated with surgery likely to have further disease develop in the neck. As highlighted in this article, this finding is likely to be a function...
of year of treatment. Surgery tended to be performed earlier in the series, when occult regional disease was not treated electively. On the other hand, radiotherapy tended to be the treatment of choice for early disease later on in the series. By then, the concept of treating first echelon nodes in supraglottic cancer was well established in the United Kingdom. The results suggest that treating first echelon nodes in supraglottic cancer reduces the risk of the later development of regional disease. It should be pointed out, however, that there is no statistical evidence that elective treatment or careful follow-up is superior in terms of tumor-specific survival. Nevertheless, most head and neck surgeons and radiotherapists agree that the balance of the argument is in favor of elective treatment.28

Given that there is equality of survival between the two treatments, other factors must also be considered in determining treatment, particularly quality of life and cost. Foote et al29 showed that when patients with early glottic cancer were treated with irradiation as opposed to transoral endoscopic resection or partial vertical hemilaryngectomy, fewer patients required retreatment. When considering overall costs, radiotherapy was marginally more expensive than transoral endoscopic removal but considerably cheaper than partial laryngeal surgery. They also found that radiotherapy resulted in superior voice quality compared with partial laryngeal surgery.

This study was not designed to investigate voice quality per se after treatment by the two modalities. Nevertheless, because of the importance of voice in determining a patient’s quality of life and because both radiotherapy and surgery are equally effective at curing disease, it is obviously crucial to examine this issue. We found, even in a small, randomized sample, that radiotherapy was overwhelmingly superior to surgery at preserving speech and voice. Other areas of laryngeal function not examined in this article include swallowing, lower airway protection, and pain.

Koufman30 and McGuirt et al31 found that voice quality after endoscopic excision was normal to mildly abnormal, but Fex and Fex32 and Elner and Fex33 showed that voice quality after endoscopic laser excision had permanently deteriorated. Other authors have also demonstrated poor voice quality after endoscopic laser treatment,34,35 whereas Lehman et al36 and Schuller et al37 reported that their patients subjectively assessed their voices as near normal after radiotherapy. The finding of better voice quality after radiotherapy compared with endoscopic laser treatment has been confirmed by other authors.38,39

When patients are given the treatment options without bias by an independent person, Dinardo et al40 found that they were less likely to choose surgery than if it were suggested by the physician. The same study also shows that more recently trained head and neck surgeons are more likely to support patient choice, with the result that conservation surgery of the larynx might be used less frequently as the treatment for early laryngeal cancer in North America. This would seem to be confirmed by an article by Shah et al41 looking at patterns of care for cancer of the larynx in the United States. They found that the proportion of cases treated with surgery alone had decreased notably in 1990–1992 compared with 1980–1985. A concurrent increase was noted in the use of radiotherapy (alone or with surgery or chemotherapy). Although not specific to early laryngeal cancer, it was postulated that the changes reflected an increased use of radiotherapy in the treatment of early laryngeal cancer and chemoradiation for patients with more advanced disease.

CONCLUSION

In the United Kingdom as in the rest of Northern Europe, irradiation has become the treatment of choice for early (T1–2, N0) laryngeal cancer. We believe this change in treatment emphasis, as highlighted in this article, is due to the equality of treatments regarding cure but the great superiority of radiotherapy at preserving speech and voice.

We consider that this article provides robust evidence to support this treatment policy. Our findings are summarized below:

1. Both radiotherapy and surgery have the same cure rate.
2. Both modalities have equality in local control.
3. In this series, radiotherapy was superior to surgery in controlling the neck. We consider that this finding is a function of treatment philosophy between surgical oncologists and radiotherapist at the time patients we recruited. It is not due to any inherent superiority of radiotherapy in regional control.
4. There was no difference between the efficacy of treatments when data were stratified for T-stage or subsite.
5. Speech and voice quality were normal or good in all radiotherapy patients studied. The outcome
of surgery in this area was disappointing, with only 3 of 10 patients having a good voice.

REFERENCES