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Laryngeal Cancer in the United States: Changes in Demographics, Patterns of Care, and Survival

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Background: **Survival has decreased among patients with laryngeal cancer during the past 2 decades in the United States. During this same period, there has been an increase in the nonsurgical treatment of laryngeal cancer.** ***Objective:*** **The objectives of this study were to identify trends in the demographics, management, and outcome of laryngeal cancer in the United States and to analyze factors contributing to the decreased survival.** ***Study Design:*** **The authors conducted a retrospective, longitudinal study of laryngeal cancer cases.** ***Methods:*** **Review of the National Cancer Data Base (NCDB) revealed 158,426 cases of laryngeal squamous cell carcinoma (excluding verrucous carcinoma) diagnosed between the years 1985 and 2001. Analysis of these case records addressed demographics, management, and survival for cases grouped according to stage, site, and specific TNM classifications.** ***Results:*** **This review of data from the NCDB analysis confirms the previously identified trend toward decreasing survival among patients with laryngeal cancer from the mid-1980s to mid-1990s. Patterns of initial management across this same period indicated an increase in the use of chemoradiation with a decrease in the use of surgery despite an increase in the use of endoscopic resection. The most notable decline in the 5-year relative survival between the 1985 to 1990 period and the 1994 to 1996 period occurred among advanced-stage glottic cancer, early-stage supraglottic cancers, and supraglottic cancers classified as T3N0M0. Initial treatment of T3N0M0 laryngeal cancer (all sites) in the 1994 to 1996 period resulted in poor 5-year relative survival for those receiving either chemoradiation (59.2%) or irradiation alone (42.7%) when compared with that of patients after surgery with irradiation (65.2%) and surgery alone (63.3%). In contrast, identical 5-year relative survival (65.6%) rates were observed during this same period for the subset of T3N0M0 glottic cancers initially treated with either chemoradiation or surgery with irradiation.** ***Conclusions:*** **The decreased survival recorded for patients with laryngeal cancer in the mid-1990s may be related to changes in patterns of management. Future studies are warranted to further evaluate these associations.** ***Key Words:*** **Laryngeal cancer, NCDB, treatment, survival.**

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INTRODUCTION

The most recent large survey of the patterns of care of laryngeal cancer in the United States was published in 1997 and compared treatment modalities between the periods 1980 to 1985 and 1990 to 1992 for 16,936 cases.[1] That report was generated through a retrospective review of individual patient records designed to answer specific questions using a mechanism supported by the Commission on Cancer (CoC).[2] Among the 1,800 acute care hospitals invited to submit cases, 769 hospitals provided data. A key finding was the change in the initial treatment of laryngeal cancers between these two time periods. Chemoradiation, irradiation alone, and the combination of surgery with irradiation increased, whereas the use of surgery alone as the initial management decreased. Data were not reported to track specific changes in management based on site and TNM classification.

Improvements in computing leading to better data collection and reporting have permitted more timely analysis of contemporary trends. The Surveillance, Epidemiology, and End Results (SEER) Program and the National Cancer Data Base (NCDB) have benefited from these advances. The SEER program is a government-sponsored

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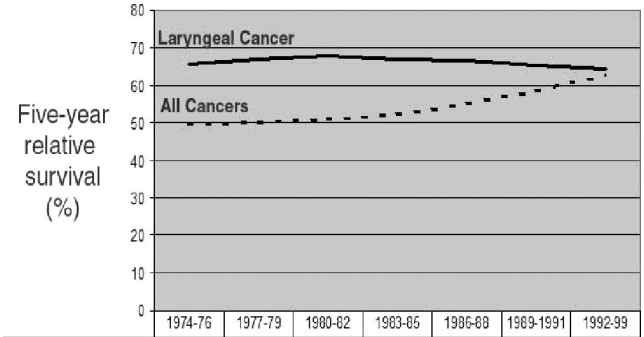

	1974-76	1977-79	1980-82	1983-85	1986-88	1989-1991	1992-99
Laryngeal Cancer	65.7	67	68.1	67.1	66.7	65.5	64.7
All Cancers	49.6	50.1	51	52.5	55.3	58.8	63

Fig. 1. Despite improvement identified overall for all cancer types, survival among patients with laryngeal cancer has diminished. Data from SEER Cancer Statistics Review, 1975–2000. Bethesda, MD: National Cancer Institute; 2003. Available at: http://seer.cancer.gov/csr/1975_2000.

registry that currently publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the U.S. population. SEER registry data are available online[3] and have been summarized in a recent journal publication.[4] These sources identified an increase in 5-year survival for 23 of the 24 cancer types evaluated between the earlier period (1983–1985) and later period (1992–1999). The single cancer type that showed a decrease in survival across these time periods was laryngeal cancer. Five-year relative survival for patients with laryngeal cancer diminished from 68.1% (1980–1982) to 64.7% (1992–1999) (Fig. 1).

To further evaluate this trend toward worsening survival and to identify concurrent changes in demographics and treatment, we reviewed the laryngeal cancer cases recorded in the larger NCDB. The NCDB is a hospital-based oncology data set that currently captures 75% of all newly diagnosed cancer cases in the United States. This database currently contains information on more than 15 million cases from 1985 to 2002 for all types of cancers. The NCDB was jointly established in 1989 by the American College of Surgeons' Commission on Cancer (CoC) and the American Cancer Society.[5] It is designed to provide descriptive information about the demographic, management, and outcomes variables characterizing cancers involving all ethnic groups in the United States.[6] The intent of this report is to analyze data from the NCDB to evaluate the survival, demographics, and patterns of management of laryngeal squamous cell carcinoma (SCC) in the United States. The following specific hypotheses are addressed.

Overall Survival Hypothesis: *The NCDB findings confirm the SEER findings that survival for laryngeal cancer has decreased in the 1990s.*

Database Artifact Hypothesis: *The NCDB is compromised by a sampling artifact (e.g., incomplete data) to account for the changes recorded across the years of study.*

Stage Distribution Hypothesis: *The worsening survival identified for laryngeal cancer correlates with an increasing incidence of advanced-stage disease.*

Demographics Hypothesis: *The increased proportion of indigent and minority patients recorded in the NCDB in the more recent period accounts for the worse survival identified in the 1990s.*

Treatment Hypothesis: *Change in initial management by use of less effective treatment has resulted in worse survival through the following:*

1. *Expanded use of nonsurgical organ-preservation strategies;*
2. *Expanded use of endoscopic surgical management; and*
3. *Less aggressive surgical management of neck metastases.*

Specific Survival Analysis Hypothesis: *Survival analysis stratified by specific site and TNM classification across the years of treatment identifies differences useful to direct future investigation.*

Specific (T3N0M0 Laryngeal SCC) Survival by Treatment Hypothesis: *The decreased survival identified for T3N0M0 laryngeal SCC correlates with increased use of nonsurgical treatment.*

Specific Analysis for T3N0M0 Glottic Squamous Cell Carcinoma Hypothesis: *The decreased survival identified for T3N0M0 glottic SCC correlates with increased use of nonsurgical treatment.*

MATERIALS AND METHODS

Case Selection

A longitudinal study of hospital-based cancer registry data reported to the NCDB was undertaken. All patients (158,426) who were diagnosed with laryngeal SCCs (excluding verrucous carcinoma) between the diagnostic years 1985 and 2001 and were treated and/or diagnosed at the reporting facility were included in this study. Cases included patients with first primaries and subsequent primaries.

Data Collection and Extraction

Until the year 1995, annual data submission from cancer registrars to the NCDB was voluntary and open to all cancer facilities. Since 1996, this data submission has been a requirement of the CoC Approvals Program and has been restricted to approved facilities. Participating hospitals provide reports on primary cancers that were diagnosed and/or treated at their institute. To ensure that the database does not include more than one record for each patient (e.g., a patient having received primary treatment at two different reporting hospitals), an algorithm based on patient and disease characteristics is used to identify and remove duplicate records.

Data were recorded according to schema published in the *Registry Operations and Data Standards (ROADS) Manual*,[14,15] the second through the fifth editions of the *AJCC Manual for Staging of Cancer*.[16–19] Standard conversion routines were used to represent tumor morphology consistent with the third edition of the *International Classification of Disease for Oncology* (ICD-O 3).[20] Cases of laryngeal SCC were extracted from the NCDB data set based on the ICD-O 3 site and histologic codes. In accordance with site groupings from the 5th edition of the AJCC staging

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manual, the topography codes for the larynx (C32) included the following subsites: glottis (C32.0), supraglottis (C32.1), subglottis (C32.2), laryngeal cartilage (C32.3), overlapping lesion of larynx (C32.8), and larynx not otherwise specific (NOS) (C32.9). Anterior surface of epiglottis (C10.1) was included as a supraglottic site. Squamous cell carcinoma included the ICD-O 3 histologic codes (M8050–8084). The variant verrucous carcinoma (M8051) was omitted because this small minority of cases is thought to behave differently from other variants of SCC and receives different treatment.[7]

Income was inferred for each patient based on the 1990 median household income of the zip code of residence and was categorized into quartiles. This crude estimate of socioeconomic status (SES) is determined indirectly by the assigning to each case the average income of households within the zip code recorded for that case. The 1990 census data were used because the data used in this review spanned 1990. The change in dollar value across the years, as is often adjusted according to the consumer price index, is not factored into this review.

Data Analysis

Combined stage is used in this article for both the stage grouping and the individual TNM classifications. This variable corresponds to pathologic staging (pAJCC stage group) when available and clinical stage (cAJCC stage group) when pathologic stage was not recorded or not appropriate. In addition to using stage groupings (0, I, II, III, IV), more detailed analyses are performed on the following specific TNM classifications: TisN0M0, T1N0M0, T2N0M0, T1 to 2N+M0, T3N0M0, T4N0M0, T3N+M0, T4N+M0, and anyTanyNM1. The TNM classifications of TisN0M0, T1N0M0, and T2N0M0 defined "early stage." All other TNM classifications defined "late stage."

Treatment in this report represents the first course of cancer-directed therapy used to manage the tumor. Subsequent therapy to address recurrences is unavailable for this report. Initial cancer-directed therapy may include a combination of modalities and may span many weeks or several months if irradiation or multiple cycles of chemotherapy are included in the original treatment plan. Treatment is presented for all laryngeal subsites, T3N0M0 laryngeal cancer (all subsites), as well as for T3N0M0 glottic SCC. These T3N0M0 cancers were chosen for further analysis because of the identified shift in management across the years of study and because these cancers are sufficiently common as to permit review of adequate numbers for statistical analysis.

The recording of specific data addressing type, timing, and dose of chemotherapy and irradiation was not sufficiently complete in the NCDB to permit detailed analysis of these parameters for the years under review. Data addressing the type of primary site surgery are sufficiently detailed to permit a broad analysis of extent of surgery for all laryngeal cancer sites. The updates to the NCDB occur in 5-year increments and, for that reason, the years 1986, 1991, 1996, and 2001 were chosen for this analysis. The categories of classification that were considered sufficiently vague as to reflect "unknown" were not included in the presentation and included "local tumor destruction not otherwise specified (NOS) (without path specimen)," "pharyngectomy, NOS," "pharyngectomy with mandibulectomy, NOS," "radical pharyngectomy, NOS," "laryngectomy, NOS," "surgery NOS," and "unknown if cancer-directed surgery done, death certificate only." These vague categories combined to total only 3.1% of cases for the diagnostic year 2001. To simplify interpretation the categories "total or radical laryngectomy, NOS" and "pharyngolaryngectomy" were condensed into the single category "total laryngectomy." The three other categories were "no surgery," "local tumor excision, NOS (with path specimen)," and "partial excision primary site, NOS subtotal/partial (hemilaryngectomy)."

Before 1994, there were no site-specific codes to describe laryngeal cancer surgery. Instead, generic categories were provided to broadly describe surgical treatment for an "all other sites" group that included the larynx. In 1994, the larynx was assigned its own site-specific surgery codes. Data addressing specific surgical approaches were reported to the NCDB beginning with the year 1985 but were not required for registry reporting until the diagnostic year 1996. As a result, a comparison across the early and later years regarding the recording of the specific surgical approach used must be approached with caution.

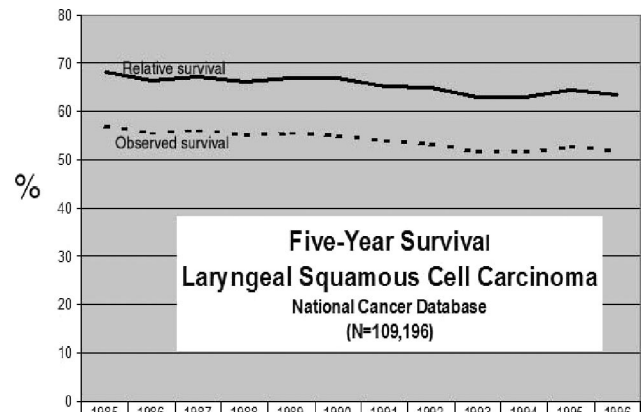
Cancer registries follow patients longitudinally and regularly update the information reported to the NCDB. This updating addresses multiple items, including the date of last contact and vital status used in survival analysis. Survival outcomes are presented as 5-year observed and relative survival rates. Observed survival denotes the actual percentage of patients that are still alive at a specified time interval after diagnosis of cancer. Relative survival was calculated by dividing the observed survival rate by the expected survival rate of persons of similar race, age, and sex. Survival analysis was limited to cases diagnosed before 1997 to permit 5-year follow up.

All analyses were performed using SPSS software (SPSS Inc., Chicago, IL). Descriptive statistics and 5-year survival estimates were generated. Outcomes were compared using the χ^2 test to test for the presence of association and the log-rank comparison to compare survival distributions.

RESULTS

Overall Survival Hypothesis: *The NCDB findings confirm the SEER findings that survival for laryngeal cancer has decreased in the 1990s.*

Analysis of the NCDB identified a decrease in survival from the 1980s to the 1990s similar to that reported from SEER (Fig. 2). Five-year relative survival for laryngeal squamous cell carcinoma recorded in the NCDB ranged from a high of 68.1% in 1985 to a low of 62.8% in 1993. Minor differences between the NCDB and SEER data may be attributed to differences in the inclusion criteria for the two studies: the NCDB analysis was restricted to SCC (excluding verrucous carcinoma), whereas the SEER analysis included all histologies. Additionally, the SEER analyses differ from this NCDB analysis by



	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
5-yr rel surv	68.1	66.4	67.1	66.2	66.9	66.9	65.3	65	62.8	62.9	64.6	63.3
5-yr obs surv	57.1	55.4	56.1	55.1	55.5	55.1	53.8	53.4	51.6	51.6	52.7	51.9

Fig. 2. Survival for patients with laryngeal squamous cell carcinoma within the NCDB decreased progressively from the mid-1980s to the mid-1990s.

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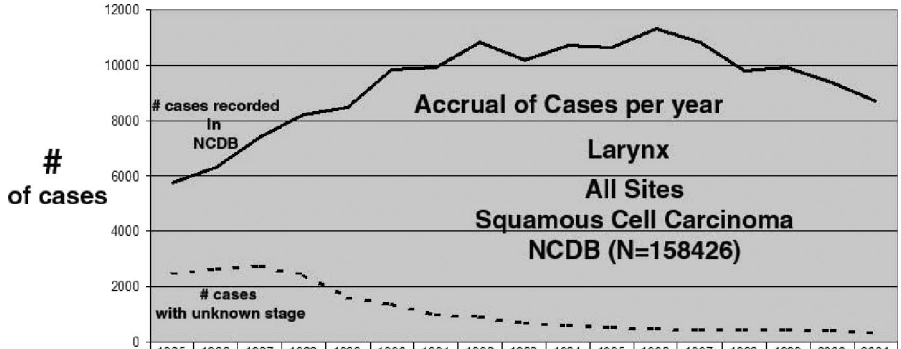

	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Total Cases	5731	6349	7453	8200	8450	9850	9944	10835	10213	10729	10639	11345	10831	9783	9941	9404	8729
Unknown Stage	2474	2648	2747	2417	1621	1410	949	907	654	590	523	484	424	432	426	402	322

Fig. 3. Staging data for laryngeal squamous cell carcinoma within the NCDB has become more complete in recent years.

excluding cases of laryngeal cancer identified in patients with a history of another previous or concurrent cancer.

Analysis. *The hypothesis is supported by the data.*

Database Artifact Hypothesis: *The NCDB is compromised by a sampling artifact (e.g., incomplete data) to account for the changes recorded across the years of study.*

The number of laryngeal SCC cases recorded in the NCDB markedly increased during the first 5 years (Fig. 3). This initial increase in number of recorded cases is most likely the result of an increase in the number of cancer programs submitting data to the NCDB. The subsequent decrease in the number of laryngeal cancer cases recorded for the more recent years parallels the decrease in number of laryngeal cancer cases estimated in the United States by the SEER data set for this same period. A substantial decrease in the number of unstaged cases was recorded during the first 6 years under review.

The dominance of glottic cancer (51% of cases) in this NCDB analysis mirrors the distribution of cases as has been reported in the United States in the past[8] (Fig. 4). Among the 9% of cases reported as "larynx, NOS," the majority is advanced stage and therefore may largely reflect extensive tumor with transglottic spread that precludes meaningful assignment of a single subsite of origin.

Analysis. *Incomplete data recording in the earlier years has improved across the years of study. Analysis of the data does not identify whether an unbalanced sampling of cases between the earlier and later periods accounts for the noted changes in survival.*

Stage Distribution Hypothesis: *The worsening survival identified for laryngeal cancer correlates with an increasing incidence of advanced stage.*

An increase in the number of stage I and IV cases relative to stage II and III cases occurred across the years of the study (Fig. 5A). Further analysis was done to determine the proportion of "late-stage" and "early-stage" cases among those with known TNM classification. Other than a 2.3% point increase in the proportion of "late-stage" cases from 1985 (38.8%) to 1987 (41.1%), the proportion of "late-stage" cases per year varied by fewer than two percentage points from the 41.2% recorded in 2001 (Fig. 5B).

Analysis. *A shift to a greater representation of advanced stage across the years of study was not identified.*

Demographics Hypothesis: *The increased proportion of indigent and minority patients recorded in the NCDB in the more recent years accounts for the worse survival identified in the 1990s.*

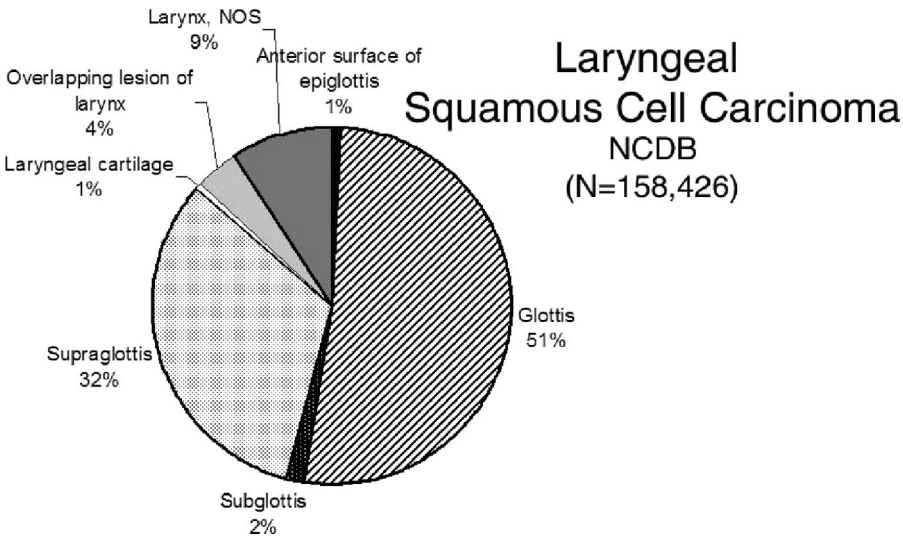

Fig. 4. Cancers isolated to the glottic larynx account for approximately one-half of all laryngeal cancer cases in the United States.

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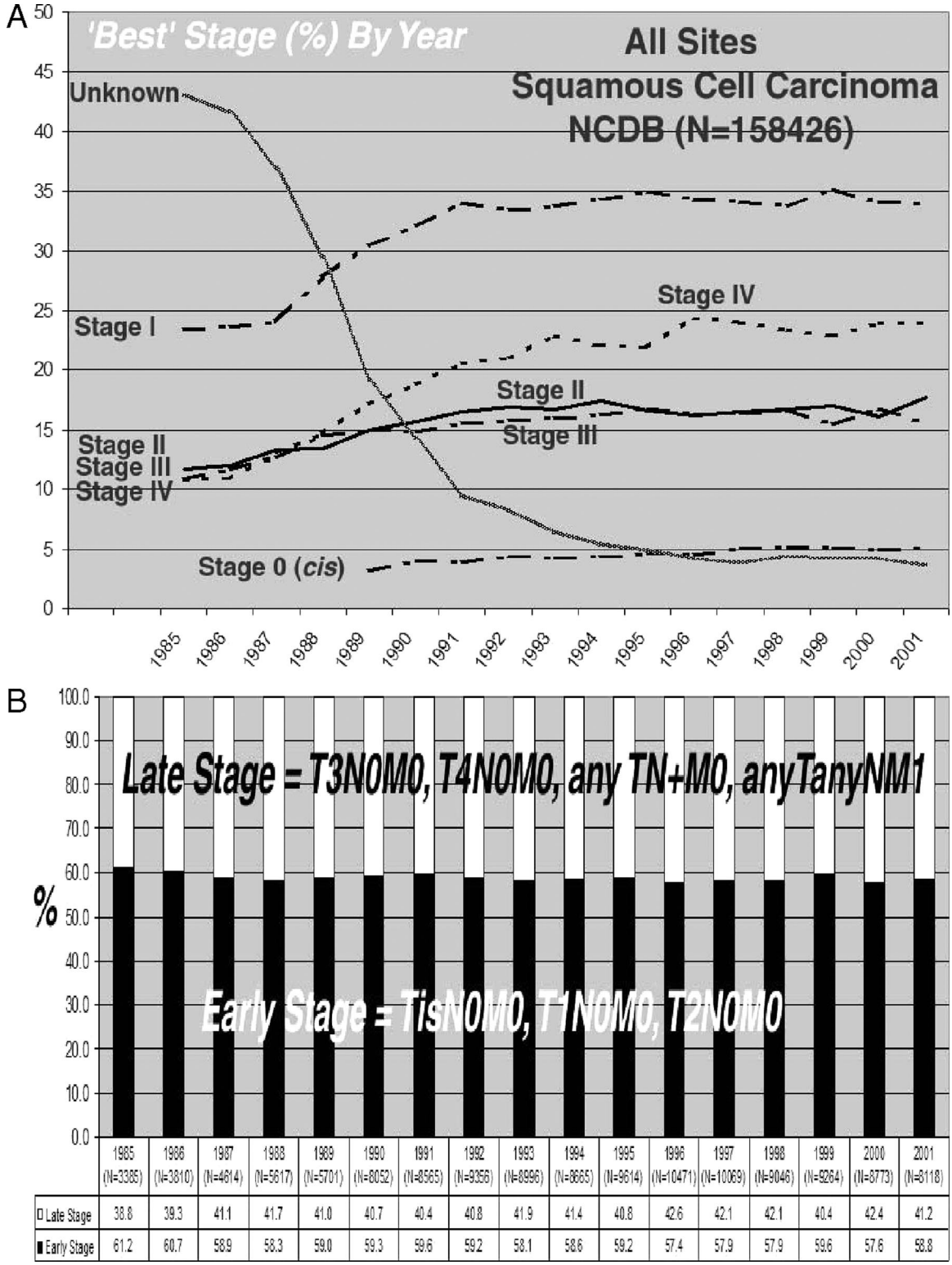

Fig. 5. (A) Notable improvement in the recording of stage occurred across the first 6 years of the NCDB. Stage I and IV cases increased to a greater degree than did stage II and III cases across the early period of study. (B) Proportion of cases per year grouped as "early" versus "late." All laryngeal squamous cell carcinoma cases recorded with known TNM classification in the NCDB were included.

Minority representation within the group of patients with laryngeal cancer increased across the years of the study (Fig. 6A). Significant changes in racial/ethnicity distribution ($P < .05$) occurred across the years of study within the white, black, Hispanic, and "other/unknown populations."

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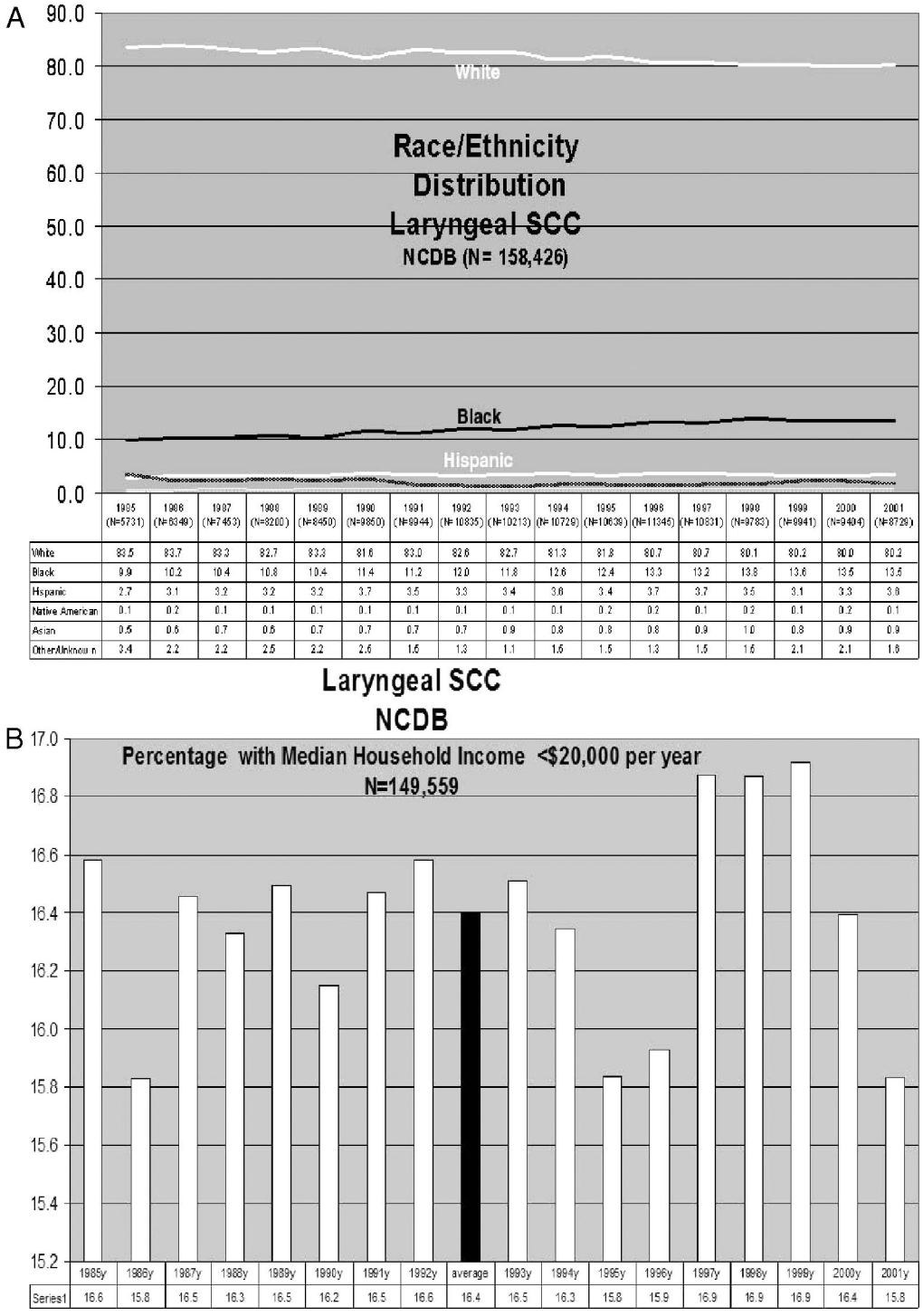

	1985 (N=5731)	1986 (N=6349)	1987 (N=7453)	1988 (N=8200)	1989 (N=8450)	1990 (N=9850)	1991 (N=8944)	1992 (N=10835)	1993 (N=10213)	1994 (N=10729)	1995 (N=10639)	1996 (N=11345)	1997 (N=10831)	1998 (N=9783)	1999 (N=9941)	2000 (N=9404)	2001 (N=8729)
White	83.5	83.7	83.3	82.7	83.3	81.6	83.0	82.6	82.7	81.3	81.8	80.7	80.7	80.1	80.2	80.0	80.2
Black	9.9	10.2	10.4	10.8	10.4	11.4	11.2	12.0	11.8	12.6	12.4	13.3	13.2	13.8	13.6	13.5	13.5
Hispanic	2.7	3.1	3.2	3.2	3.2	3.7	3.5	3.3	3.4	3.6	3.4	3.7	3.7	3.5	3.1	3.3	3.8
Native American	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.2	0.1	0.2	0.1
Asian	0.5	0.6	0.7	0.5	0.7	0.7	0.7	0.7	0.9	0.8	0.8	0.8	0.9	1.0	0.8	0.9	0.9
Other/Unknown	3.4	2.2	2.2	2.5	2.2	2.6	1.5	1.3	1.1	1.5	1.5	1.3	1.5	1.6	2.1	2.1	1.8

Fig. 6. (A) The distribution of laryngeal squamous cell carcinoma cases within the NCDB showed an increase in the minority groups across the years of study. (B) An average of 16.4% of cases occurred in low-income households and varied between 15.8% and 16.9% across the years of the study.

The low-income group included patients with annual median household incomes of less than $20,000 and represented 16.4% of the NCDB data set. The high-income group included patients with annual incomes of $32,000 or more, which represented 33.7% of the data set. The income group representing the lower quartile in median household income (less than $20,000 per year) remained stable across the years of study (Fig. 6B).

Analysis. *An increase in minority race/ethnicity representation paralleled the increased mortality across the*

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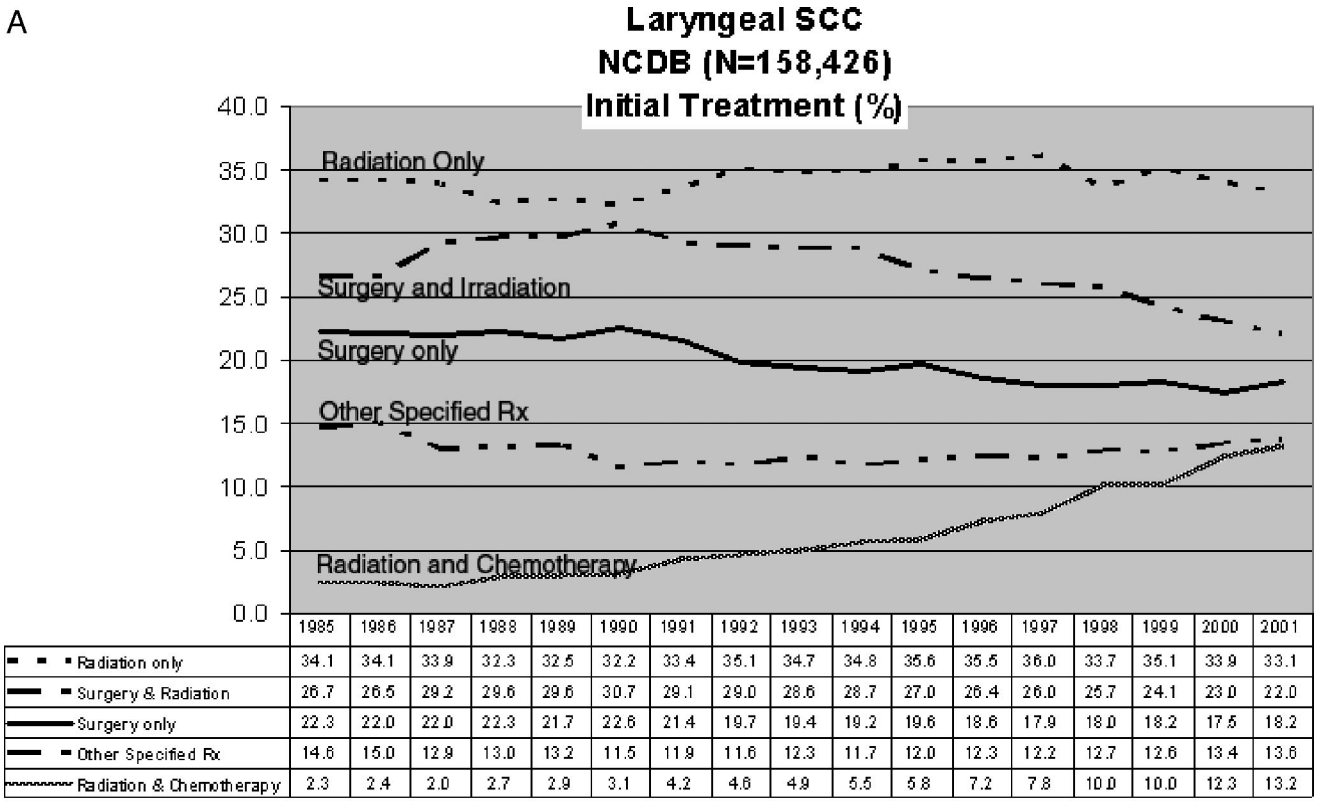
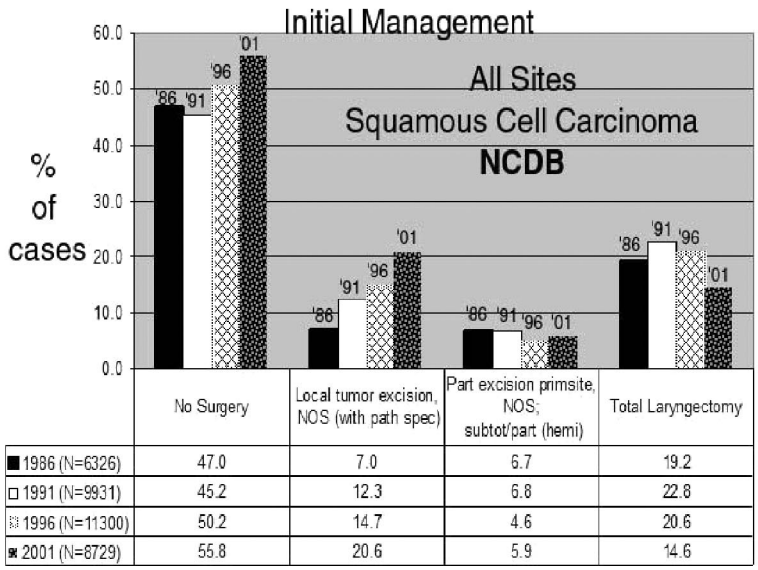
A



	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Radiation only	34.1	34.1	33.9	32.3	32.5	32.2	33.4	35.1	34.7	34.8	35.6	35.5	36.0	33.7	35.1	33.9	33.1
Surgery & Radiation	26.7	26.5	29.2	29.6	29.6	30.7	29.1	29.0	28.6	28.7	27.0	26.4	26.0	25.7	24.1	23.0	22.0
Surgery only	22.3	22.0	22.0	22.3	21.7	22.6	21.4	19.7	19.4	19.2	19.6	18.6	17.9	18.0	18.2	17.5	18.2
Other Specified Rx	14.6	15.0	12.9	13.0	13.2	11.5	11.9	11.6	12.3	11.7	12.0	12.3	12.2	12.7	12.6	13.4	13.6
Radiation & Chemotherapy	2.3	2.4	2.0	2.7	2.9	3.1	4.2	4.6	4.9	5.5	5.8	7.2	7.8	10.0	10.0	12.3	13.2

B



	No Surgery	Local tumor excision, NOS (with path spec)	Part excision primsite, NOS; subtot/part (hemi)	Total Laryngectomy
1986 (N=6326)	47.0	7.0	6.7	19.2
1991 (N=9931)	45.2	12.3	6.8	22.8
1996 (N=11300)	50.2	14.7	4.6	20.6
2001 (N=8729)	55.8	20.6	5.9	14.6

Fig. 7. (A) General treatment type by year for laryngeal squamous cell carcinoma. (B) Broad groupings of initial surgical management of the primary site.

years of study. The indirect assessment of SES showed no appreciable change during this same period.

Treatment Hypothesis: *Change in initial management by use of less effective treatment has resulted in worse survival through the following:*

1. *Expanded use of nonsurgical organ preservation strategies.*

Treatment patterns have changed across the years of study with a notable decrease in the use of "surgery" as a single modality and an increase in "chemoradiation" (irradiation with chemotherapy) as initial management (Fig. 7A). The category "other" reflects the treatment classified as either "unknown," "no cancer directed therapy," or other combinations of management including chemoradiation with surgery as well as chemotherapy with surgery.

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Survival analysis was limited to those cases diagnosed before 1997 to permit follow up sufficient for 5-year survival analysis. During this period (from 1985–1996), the proportion treated with irradiation alone remained stable between 1988 and 1990 at 32% and had increased to 35.5% by 1996. Over the same period, use of chemoradiation increased steadily from 2.0% in 1987 to 7.2% in 1996.

Analysis. *Treatment patterns have changed with an increase in nonsurgical management with irradiation alone and with chemoradiation. The increase in nonsurgical management parallels the increase in mortality across the years of study for which survival analysis was performed (1985–1996).*

2. Expanded use of endoscopic management and nonsurgical management.

Challenges in the interpretation of the recording of the specific surgical approaches are evident from the wording describing conservation laryngeal surgery (Fig. 7B). Although the term "local tumor excision, NOS (with path specimen)" is not synonymous with endoscopic resection, in more recent years, this specific code has been most commonly used to record endoscopic resection. The term "part excision primsite, NOS; subtot/part (hemi)" (partial excision of primary site, NOS; subtotal/partial [hemilaryngectomy]) is generally considered synonymous with a partial or subtotal laryngectomy. Interpretation of the codes that reflect total laryngectomy is more clear and shows a decrease in use of total laryngectomy in the most recent period. This finding correlates with an increase in treatment labeled as "no surgery."

The completeness in recording initial management by the four selected treatment categories listed in Figure 7B has improved from the earlier to the later period. For the diagnostic year 1986, 20.1% of cases were coded by categories that failed to assign a specific surgical type. Across the years of the study, this proportion of unassigned cases progressively decreased to reflect only 3.1% of the cases in the 2001 year. The category "unknown if cancer-directed surgery done, death certificate only" averaged 1.5% of cases across the years, ranging from a high of 2.9% in 1985 to a low of 0.1% in 2001.

Analysis. *The trend toward increasing nonsurgical treatment paralleled the trend of decreasing survival. The completeness of data addressing surgical approaches within the NCDB and the use of ambiguous coding schemes until the more recent years prevent meaningful analysis of the available data to further address this hypothesis.*

3. Less aggressive surgical management of neck metastases.

The data addressing lymphadenectomy in the NCDB indicate a gradual increase in the proportion of cases reported as "no regional lymph nodes removed" rising slightly from 75.7% in 1985 to 78.2% in 1996. Further analysis showed that this trend reversed when cases reported as "unknown" were removed with a larger proportion identified with "no regional lymph nodes removed" in 1985 (85.9%) than in 1996 (84.4%). From this analysis, it is apparent that the data within the NCDB addressing

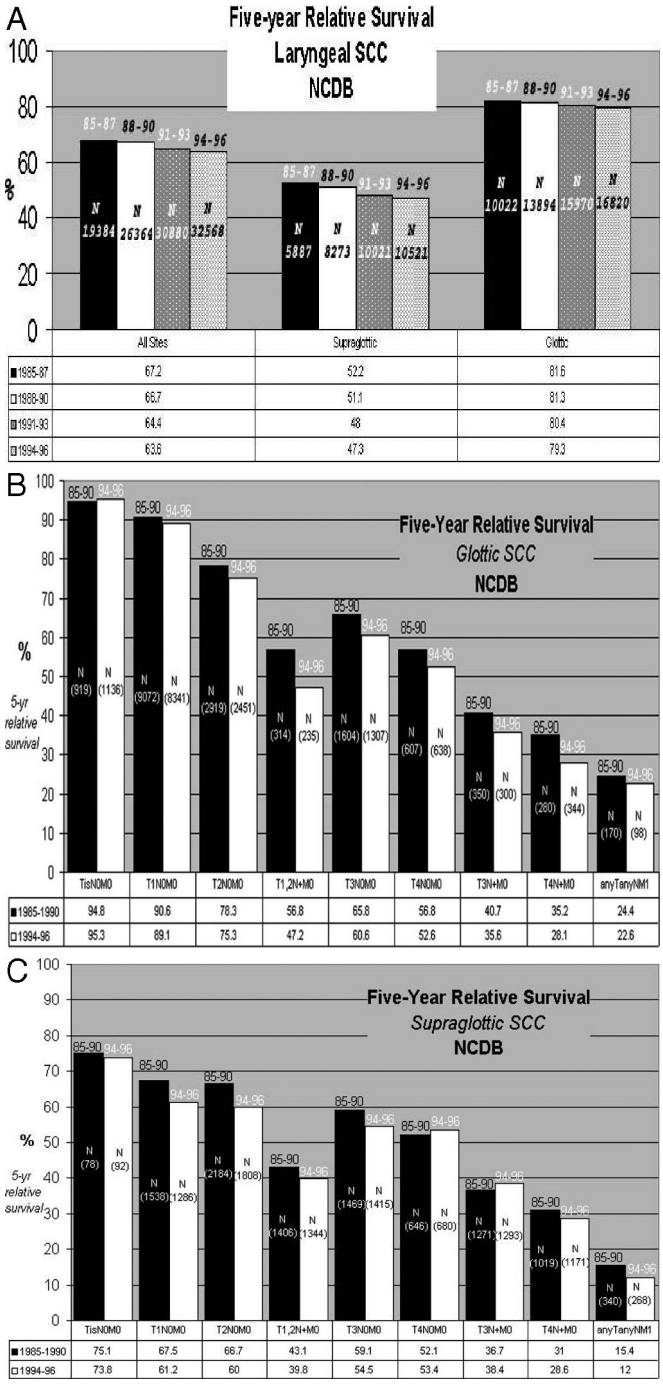

Fig. 8. (A) Five-year relative survival by site and year grouping permitted analysis of groups ranging from a low number (N) of 5,887 for supraglottic cancers from 1985 to 1987 to a high (N) of 32,568 representing all laryngeal squamous cell carcinoma cases from 1994 to 1996. (B) Five-year relative survival calculated between the early (1985–1990) period and later period (1994–1996) for glottic cancer. The number of cases (N) was lowest for the classification "anyTanyNM+" for the later period (N = 98) and largest for the classification "T1N0M0" for the earlier period (N = 9,072). (C) Five-year relative survival calculated between the early (1985–1990) period and later period (1994–1996) for supraglottic cancer. The number of cases (N) was lowest for the classification "TisN0M0" for the early period (N = 78) and greatest for the classification "T2N0M0" (2184) for the early period.

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extent of lymphadenectomy is not currently recorded in sufficient detail to permit meaningful analysis.

Analysis. *Data within the NCDB is not sufficiently complete to address this hypothesis.*

Specific Survival Analysis Hypothesis: *Survival analysis stratified by specific site and TNM classification identifies differences across the years of the study useful to direct future investigation.*

Analysis condensed into 3-year periods identified a progressive decrease in survival that affected supraglottic cancer more than glottic cancer (Fig. 8A). A statistically significant decrease ($P < .05$) occurred in comparing the relative survival for both "all sites" and the supraglottis between the two earlier periods (1980s) and the two later periods (1990s). The smaller decrease in survival for glottic SCC reached statistical significance only for the comparison between the 1985 to 1987 period and the 1994 to 1996 interval.

A comparison of survival for selected TNM groupings for glottic SCC identified a decrease in survival from the earlier (1985–1990) to later (1994–1996) period for all except the category TisN0M0 (Fig. 8B). The decline in survival appeared to be smaller for the early stages and more striking for the advanced stages.

A comparison of survival for selected TNM groupings for supraglottic SCC identified a decrease in survival from the earlier (1985–1990) to later (1994–1996) period for all except the categories T4N0M0 and T3N+M0 (Fig. 8C). In contrast to the findings for glottic cancer, the most striking decline in survival occurred among the early-stage supraglottic cancers with the classifications T1N0M0 and T2N0M0. A notable decline in survival also occurred for the T3N0M0 (stage III) supraglottic cancer cases.

Analysis. *Survival varied according to specific TNM classifications in patterns useful to direct further investigation.*

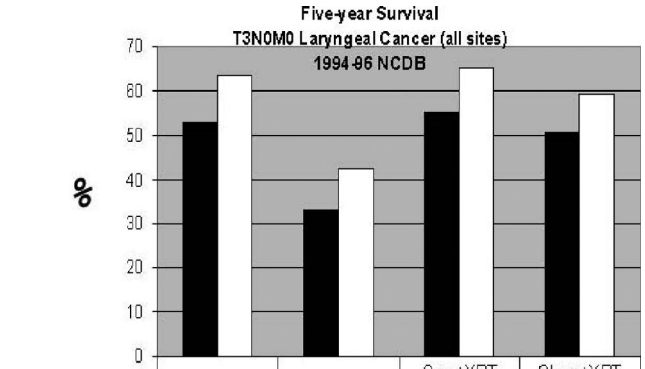

Fig. 9. Five-year observed and relative survival for T3N0M0 laryngeal squamous cell carcinoma showed the best outcome for those patients whose initial management was with surgery either alone or combined with irradiation.

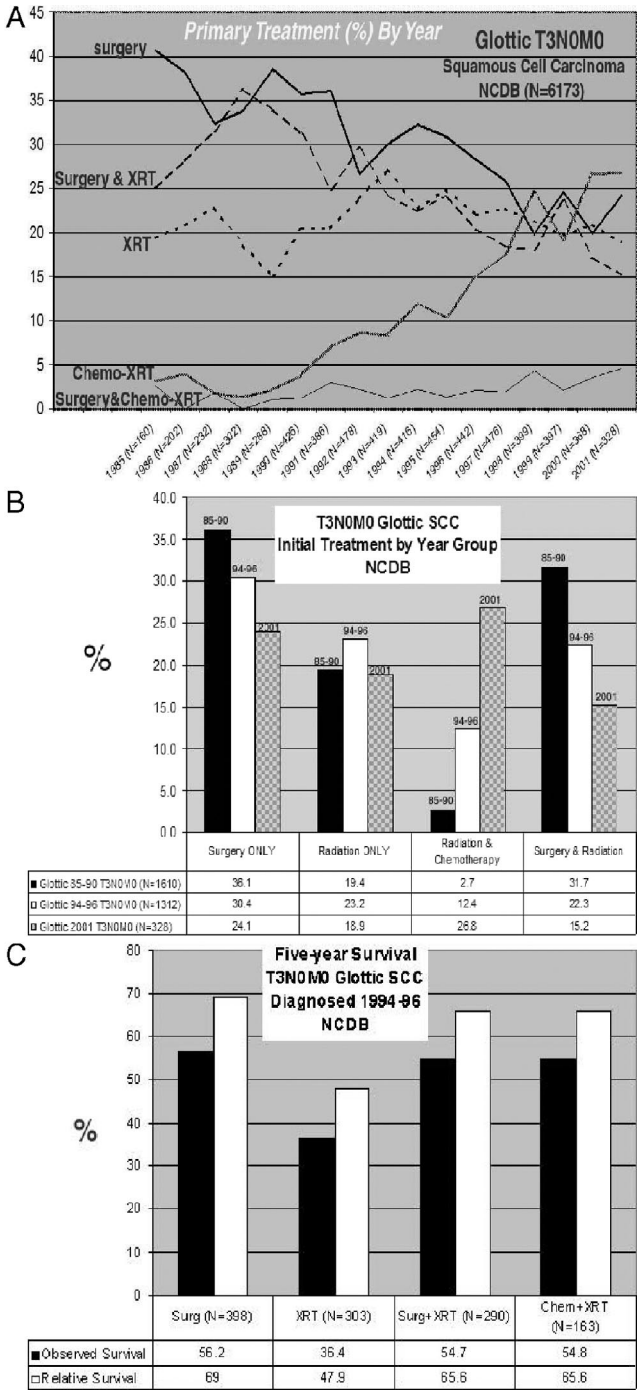

Fig. 10. (A) Chemoradiation became the most common initial treatment for T3N0M0 glottic squamous cell carcinoma in 1999. (B) Comparative analysis of treatment of T3N0M0 glottic squamous cell carcinoma for the 1994–1996 period with an earlier and later period offers perspective for subsequent survival analysis for this period. (C) Initial treatment of patients from the 1994–1996 period with T3N0M0 glottic squamous cell carcinoma resulted in identical 5-year relative survival (65.6%) after treatment with either surgery and irradiation or chemoradiation.

Specific (T3N0M0 Laryngeal SCC) Survival by Treatment Hypothesis: *The decreased survival identified for T3N0M0 laryngeal SCC correlates with increased use of nonsurgical treatment.*

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Survival analysis for T3N0M0 laryngeal SCC included all sites within the larynx: glottic, subglottic, supraglottic, overlapping sites, laryngeal cartilage, and unspecified site (Fig. 9). For this broad group, statistically significant better 5-year relative survival was seen for those patients treated surgically (with or without irradiation) (64.4%) compared with those treated with irradiation (with or without chemotherapy) (49.4%) ($P < .05$).

Generation of relative survival rates permitted comparison of 95% confidence intervals to determine significance ($P < .05$). For relative survival comparisons showing overlap in 95% confidence intervals ($P > .05$), further comparative analysis addressing observed survival was done to generate specific P values. Direct analysis between the observed 5-year survival of 59.3% for chemoradiation was not significantly different from the 63.3% of surgery alone ($P = .503$) and showed borderline significance compared with the 65.2% of surgery with irradiation ($P = .067$). Observed survival for patients treated with radiation alone was statistically worse in comparison to survival after treatment with each of the other options ($P = .000$).

Analysis. *Poorer survival for T3N0M0 laryngeal SCC followed treatment that did not include surgery. The subset of nonsurgical patients treated with chemoradiation fared better than those treated with irradiation alone.*

Specific Analysis for T3N0M0 Glottic Squamous Cell Carcinoma Hypothesis: *The decreased survival identified for T3N0M0 glottic SCC correlates with increased use of nonsurgical treatment.*

A sufficiently large number of cases permitted further analysis of the subset of T3N0M0 SCC cases isolated to the glottis. Initial treatment was analyzed by individual year (Fig. 10A). Secondary analysis of treatment by year groupings (Fig. 10B) focused on the 1994 to 1996 period to permit comparison between the earlier (1985–1990) and later (2001) periods to offer perspective regarding the selective survival analysis presented for the 1994 to 1996 period (Fig. 10C). As was noted for T3N0M0 laryngeal SCC (which included all sites), significantly worse 5-year relative survival was noted for those for T3N0M0 glottic cancers treated by the combined categories of radiation alone and chemoradiation (54.7%) compared with surgery with or without irradiation (67.5%) ($P < .05$). Five-year relative survival for those T3N0M0 glottic cancers treated with irradiation alone (47.9%) was significantly worse than for those cases treated with surgery alone (69.0%) ($P < .05$). Identical 5-year relative survival (65.6%) was noted after initial treatment with chemoradiation and surgery combined with irradiation.

Analysis. *Nonsurgical treatment is associated with significantly worse survival for T3N0M0 glottic SCC. This poorer survival following nonsurgical treatment reflects the impact of poor survival with irradiation alone. Survival after treatment with chemoradiation was similar to that of surgical treatment for T3N0M0 glottic SCC.*

DISCUSSION

Advances in translational research and the accumulation of clinical experience continually modify the way cancer is treated. The efficacy of these modifications has traditionally been assessed by analysis with survival as the end point. This survival analysis using data from the NCDB suggests that the modifications introduced in management of laryngeal cancer may have been less effective in the 1990s than they were in the 1980s.

The assessment of treatment efficacy is not restricted to survival analysis. Over the past 2 decades, increasing emphasis has been placed on other parameters such as functional status, organ preservation, cost of treatment, and quality of life. A focus of contemporary clinical investigation has been the study of treatments designed to preserve laryngeal function for patients with advanced laryngeal cancers traditionally treated with total laryngectomy. A frequently cited study by McNeil et al. used a questionnaire administered to healthy individuals and concluded that some would forego total laryngectomy in favor of alternative therapy even if this choice diminished their chance for cure.[9] A subsequent prospective, randomized analysis of 332 patients published in 1991 (Department of Veterans Affairs [VA] Laryngeal Cancer Study Group trial or VA Laryngeal Cancer Study) reported that induction chemotherapy followed by radiotherapy permitted the successful treatment of a subset of patients with advanced laryngeal cancers without laryngectomy and without diminishing the chance for cure.[10] This finding has led some clinicians to relegate surgical treatment to a secondary role as salvage therapy with the comment that it "would appear that there is no longer any reason to do a total laryngectomy as the initial treatment for laryngeal cancer."[11] The timing of the initial publication from the VA Laryngeal Cancer study correlates with the expanded use of chemoradiation as well as irradiation alone as treatment for laryngeal cancer in the United States (Figs. 7A and 10A).

This timing also correlates with decreased survival among patients with laryngeal cancer. The VA Laryngeal Cancer study showed no difference in 2-year survival between treatment arms ($P = .9846$). In contrast, the NCDB data favored initial treatment of T3N0M0 laryngeal SCC with surgery and irradiation (65.2% 5-year relative survival) compared with chemoradiation (59.2% 5-year relative survival) with differences in 5-year observed survival that bordered on statistical significance ($P = .067$). In this NCDB review, better survival was noted for T3N0M0 laryngeal SCC treated with surgery than without ($P < .05$). This finding does not necessarily mean that nonsurgical treatment is less effective than surgical treatment. This difference in outcome may result from the method by which treatment was selected. Poor outcome would be expected from treatment with irradiation if it were more commonly chosen for patients with diminished life expectancy from comorbidities or synchronous malignancies such as an incurable lung cancer. The VA Laryngeal Cancer study selected patients by strict criteria and then randomized them to treatment. In contrast, unknown selection biases determined the treatment choices recorded in the NCDB. The influences that may direct management decisions in an unbalanced (nonrandom) way include comorbidities, functional status, patient preference, physician preference, and subtle differences in tumor extent that are not captured by the AJCC staging system.

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The poorer comparative outcome identified for chemoradiation reported from the NCDB study when compared with the VA Laryngeal Study may reflect the impact of treatment observed outside of a clinical trial. It is likely that results reported from clinical trials conducted at high-volume institutions with rigorous and coordinated controls identify a better outcome than might be obtained in the general community. During the mid-1990s, the majority of cases submitted to the NCDB came from community hospitals (60%), approximately one-third from teaching cancer programs (30%), and less than 10% of cases from other cancer programs. The concept that institutions that treat a large number of patients offer better coordinated treatment than institutions with lower volumes has been supported by retrospective studies and, more recently, by a reanalysis of the results of a prospective study. A multicenter randomized, prospective study from Italy[12] showed combined chemoradiation to be more effective than radiation alone for advanced head and neck SCC. This study was then reevaluated to determine the impact of treatment location on outcome.[13] The authors indicated that outcome for patients treated with chemoradiation at eight ancillary facilities was worse than observed at the single coordinating center where the majority of patients were treated. The authors suggest that "the lack of a close interaction among specialists necessary to warrant the optimal support to patients" as well as the absence of a concentrated experience with treatment at these ancillary locations led to the poorer outcomes.

It is encouraging that analysis using the NCDB of the more specific T3N0M0 SCC localized to the glottis showed identical 5-year relative survival (65.6%) after initial treatment with either chemoradiation or surgery with irradiation (Fig. 10C). This finding, in the context of the worse survival seen after chemoradiation for T3N0M0 laryngeal cancer overall (Fig. 9), could signal the importance of appropriate patient selection when chemoradiation is used outside of a protocol setting.

Reasons other than changes in the patterns of management occurring in the early 1990s must also be considered in analyzing the cause for the overall decline in survival identified among patients with laryngeal cancer over the past 2 decades in the United States. Support for this concept is offered from analysis of the SEER database (Fig. 1) indicating that a small decline (1.0% point) in 5-year relative survival occurred between the 1980 to 1982 and 1983 to 1985 periods. This decline predated the period of study using the NCDB and occurred at a time when chemoradiation as a primary treatment was unusual.

The demographic characteristics of patients with of laryngeal cancer have changed in the United States as indicated by the decreasing number of cases of laryngeal cancer resulting in a decrease in the number of deaths despite an increase in mortality among those who develop laryngeal cancer. Decreasing tobacco consumption in the United States has been linked to a decrease in number of both lung and laryngeal cancer cases.[14] From 1983 to 2003, a sustained decline occurred in cigarette smoking for all age groups except for persons aged 18 to 24 years and has resulted in 21.6% of adults still smoking as of 2003.[15] Analysis by level of education identified smoking prevalence to be highest among adults who had earned a GED diploma (44.4%) and lowest among those with graduate degrees (7.5%). Analysis by economic status identified the highest prevalence of smoking to occur in adults living below the poverty level (30.5%). It is reasonable to hypothesize that concentration of the laryngeal cancer among the poor and the poorly educated could be responsible for the observed decrease in survival.

Previous studies have identified a disproportionate cancer burden among minorities and lower income groups. Limited access to medical resources coupled with unfavorable environmental and behavioral factors have been linked not only to a greater risk of developing cancer, but also to treatment failure.[16–18] The decrease in the proportion of laryngeal cancer cases classified as white from approximately 83% in the mid-1980s to 80% in the late 1990s likely reflects the overall changing demographics in the United States. The increase in the black and Hispanic population in the study across this period also parallels the changing demographics of the United States. These changes occurred without an appreciable concurrent change in income distribution across the years identified in the NCDB. The proportion of cases with an estimated family median household income of less than $20,000 was similar in 1985 (16.6%) and 2001 (15.8%) and varied fewer than 1.3% points across the years of study.

Race and SES have received close scrutiny as variables influencing treatment and outcome for many types of cancers. A population-based study using the SEER database linked with the Medicare database offered a detailed evaluation of pancreatic cancer among patients 65 years and older in the United States.[19] Although race was not a factor in determining the type of treatment, SES was a determinant. Among those in the lowest socioeconomic group, only one-third of patients received treatment for their pancreatic cancer, whereas more than one-half of the patients in the top socioeconomic stratum received treatment. These investigators identified that limited access to payment for health care is not the only factor that may compromise care for lower the lower socioeconomic group. Differences in attitudes toward medical care as well as logistic issues regarding access to the treatment facilities may play a role. It is noteworthy that, among patients with identical insurance coverage, those in the lower socioeconomic group were still less likely to receive effective care in this pancreatic cancer study.

The 3.5% percentage point decrease in the racial grouping "white" in this NCDB analysis of laryngeal cancer correlates with an increase in the proportion of minorities. If this change in demographics were an important variable influencing survival from laryngeal cancer, it also would be expected to affect survival for other cancers that share similar epidemiology such as lung cancer. The SEER cancer statistic review between the 1983 to 1985 and the 1992 to 1999 periods in the United States identified an increase in the 5-year relative survival rates for esophageal cancer (from 8–14%), oral cavity cancer (from 53–57%), and cancer of the lung and bronchus (from 14–15%).[20] It seems unlikely that these demographic changes could account for the decreased survival for laryngeal

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cancer in the absence of a similar negative impact on survival for other cancers.

The increasing average age in the United States is a changing demographic factor that could negatively influence the observed survival trends recorded over the years. Relative survival, which adjusts computed rates according to life expectancy by patient age, race, and gender, would be expected to control for this change in patient demographics and influences outcome patterns across the years of study. The changes in the composition of the database as to race, sex, and age are therefore not likely to account for the decrease in relative survival seen across the years of study.

The NCDB has evolved since its inception with changes that could confound comparisons made between earlier and contemporary periods. The first call for data by the NCDB yielded an estimated 24% of all cancer cases in the United States in 1985.[21] The number of hospitals reporting cases to the NCDB has gradually increased to the point that an estimated 73% of cancers in the United States were recorded by the NCDB in 2001. The quality of the data within the NCDB has been studied with multiple analyses acknowledging potential sites for error in accumulating data: registrar performance in recording data, completeness and uniformity of physician documentation, computer capabilities, and adequacy of coding systems.[22–25] Escalating problems with mergers, acquisitions, and insolvencies among hospitals also have been reported as major reasons for incomplete acquisition of data from registrars.[26]

Eberle et al. reported the results of an audit of the NCDB to evaluate the consistency in the data by reabstracting data for specific tumor types. Random computer sampling targeted 30 hospitals in the Midwest region for specific review of 20 cases per hospital diagnosed in 1993. Consistency between the original report and the reabstracting was identified as 100% accurate for nine items, including age, histology, and nodal status as determined pathologically. There was less than 90% agreement on eight items, including clinical T classification (the lowest at 81%), clinical stage, surgery type, and tumor size.

Despite the potential problems in recording data accurately in a large database, comparison of results from the NCDB with other data sets generates greater confidence in the quality of the data. A recent report addressing pancreatic cancer found remarkably similar results in comparing reports from a linked SEER–Medicare data study to the NCDB.[27]

There does not appear to have been an appreciable change in distribution between early-stage and late-stage cases during the years of this NCDB study. The small (2.3% point) increase in the proportion of advanced-stage cases identified across the first 2 years of the study (1985–1987) could not account for the decreased survival observed during all years of the study (Fig. 5). It is possible that the larger proportion of unstaged cases in the earlier years of the study could induce an artifact if these cases were unbalanced in a way that did not parallel the case mix among staged cases. The staging difficulties in accurately and consistently classifying tumors according to their anatomic extent are well recognized.[28] The increasing sophistication in radiographic imaging with improvements in computed tomography and magnetic resonance imaging with the addition in more recent years of positron emission tomography imaging further confounds the interpretation of potential shifts in analysis of tumor extent and stage during the 2 decades.[29]

It is generally supported that the clinical care events that produce the greatest impact on a patient's outcome take place shortly after diagnosis and during initial therapy.[30] Although this concept likely applies to laryngeal cancer, SCC of the larynx differs from SCC at other sites of the upper aerodigestive tract in that salvage treatment for laryngeal cancer is more likely to be beneficial than salvage treatment at other sites.[31] Although limited data addressing recurrence and salvage therapy are available through the NCDB, this information is not adequate to permit meaningful analysis for this report. This analysis therefore focuses on the impact of initial management.

The difficulties in obtaining detail about specific surgical treatment preclude definitive statements about changes in the patterns endoscopic management and other partial laryngectomy approaches. The codes available to the registrars during the early years of the study did not provide sufficient detail to identify the type of conservation laryngeal surgery used. Despite improvement in data recording with the development of codes specifically targeted to characterize laryngeal cancer surgery, ambiguities persist not only in defining the type of surgery done, but also in determining whether treatment with surgery was done at all. For example, treatment that includes endoscopic resection to address a small glottic cancer would be considered definitive surgical treatment were no subsequent treatment with irradiation given. Alternatively, the same surgical case could be considered a biopsy as a preamble to definitive treatment with irradiation in which case the treatment would be recorded as radiation alone. If the treating surgeon considered the biopsy as an excisional biopsy, it would be reasonable to consider this same treatment as combined modality therapy using surgical resection with postoperative irradiation. As a result of these considerations confounding interpretation and, despite a large number of early-stage laryngeal cancer cases in this study, analysis of survival according to treatment type was limited to the category T3N0M0 for which treatment is more clearly defined.

It is conceivable that the decline in survival identified for early-stage supraglottic (and to a lesser degree, glottic) cancers could be linked to trends to perform less aggressive primary site surgery by avoiding total laryngectomy and less aggressive neck surgery by diminishing use of radical or comprehensive neck dissections. Although this review identifies that endoscopic surgical management has likely increased across the years of study, definitive statements linking patterns of specific surgical treatment at the primary site and in the neck to outcome cannot be made through analysis of the existing data set.

A CoC hypothesis-based special study dedicated to collecting clinical information not fully captured in the NCDB is planned to further investigate the impact of treatment on survival. Details addressing extent of surgery as well as nonsurgical considerations addressing dose

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and type of chemotherapy and radiation are targeted for examination. The availability of these types of special studies coupled with the continuing improvements in the NCDB underscore the increasing value of this registry program to accurately record and report cancer care as it is practiced throughout the United States.

CONCLUSION

This review of NCDB data confirms previous reports from the SEER database identifying a decrease in survival among patients treated for laryngeal cancer from the 1980s to the 1990s.

The declining survival rate coincided with multiple other changes that occurred during this period, the most dramatic being the increase in chemoradiation, and the decrease in surgery as initial cancer management in the early 1990s. At this time, it is not possible to conclude definitively if these treatment factors are causally related or merely associated in the database. Confounding factors may be masking the effects of the different treatments on survival.

Further study is planned to provide a more detailed evaluation of the interaction of multiple variables impacting the trends displayed in this study.

Strengths and shortcomings of the NCDB are revealed in this analysis. Improvements in the database are apparent from the more complete recording of staging and treatment data in more recent years. It is anticipated that continued improvement in computing and coding will ensure a critical role for the NCDB to record and report cancer care and its outcome in the United States.

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