The Laryngoscope
Lippincott Williams & Wilkins

Impact of Second Primary Tumors on Survival in Head and Neck Cancer: An Analysis of 2,063 Cases

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Objective/Hypothesis: To investigate the impact of second primary tumors on prognosis for patients with head and neck squamous cell carcinoma (HNSCC).

Study Design: Prospectively recorded data on HNSCC patients treated at an academic tertiary referral center.

Methods: An analysis of 2,063 patients treated over a 15 year period for tumors of the upper aerodigestive tract, with a minimum follow-up of 10 years.

Results: A total of 351 (17%) patients developed a second primary, mean time to diagnosis of the second tumor being more than 4 years from the date of the initial tumor. Median overall survival from the date of the first tumor among patients who later developed a second primary was 6 years versus 3 years among all other patients ($P < .05$). During the first 6 years after treatment of the initial tumor, cancer specific survival was better in the second primary group. After diagnosis of a second primary tumor, median survival was 12 months. A positive correlation was found between second primaries and stage I/II primary disease, low patient age, and initial tumors of the larynx and oral cavity.

Conclusions: The group of patients with the highest risk of a second primary tumor was younger patients with limited initial tumors. A high proportion of patients who later developed a second primary were complete responders after treatment of the first tumor. However, prognosis was poor after the actual diagnosis of the second primary tumor.

Key Words: Second primary tumor, head and neck cancer, squamous cell carcinoma, cancer, survival, prognosis.

***Laryngoscope,* 118:1350–1356, 2008**

INTRODUCTION

The last decade's 5 year survival among patients with squamous cell carcinoma of the head and neck (HNSCC) remained at 50% despite advances in treatment strategies. Failing patients succumb to locoregional recurrence during the first 3 years after diagnosis,[1] whereas distant metastases occur in less than 10% of the patients.[2] Among those who develop a second primary tumor, as defined by Warren and Gates,[3] the reported annual incidence is 3.2% to 4%.[4–7]

The "field cancerization" hypothesis is considered the key model to explain the biological mechanism leading to second tumors.[8] According to this hypothesis, multiple nonrelated precancerous lesions may exist adjacent to the original index tumor, each with the capacity to form new tumors. A modified version of field cancerization defines "a true second primary tumor" as genetically independent of the index lesion. Alternatively, the term "second field tumor" is used when new tumors arise in the same premalignant field having genetic fingerprints similar to that of the index tumor.[9] A competing biological model is clonal expansion. Second primary tumors may present with identical genetic markers as the index tumor, indicating development from the same clone. Progenitor cells from the index tumor are thought to spread, implant, and grow at a new site.[10]

Second primary tumors were investigated among more than 2,000 patients treated for HNSCC during 15 years with a minimum of 10 years of follow-up. It was sought to evaluate what impact second primary tumors had on prognosis, aiming specifically at identifying the group of patients running the highest risk of second primary tumor development after treatment of HNSCC.

MATERIALS AND METHODS

Prospectively collected data on 2,063 patients with tumors of the oral cavity, oropharynx, hypopharynx, and larynx were used. All patients were treated from 1983 through 1997 at the Department of Otolaryngology, Head and Neck Surgery, The National Hospital, Oslo, in collaboration with the Norwegian Radium Hospital, Oslo, Norway. All cases were histologically confirmed squamous cell carcinomas. A record was made of patient age, sex, International Union Against Cancer stage and

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Editor's Note: This Manuscript was accepted for publication March 7, 2008.

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DOI: 10.1097/MLG.0b013e318172ef9a

Tumor, Node, Metastases classification, index tumor site, date of first treatment, type of treatment, date of second primary tumor diagnosis, site of second primary tumor, and date and status at last follow up.

Patient data were based on clinical examination, panendoscopy, and, in selected cases, palpation under general anesthesia. All index tumors were evaluated with CT scans, chest radiographs, and fine needle aspiration cytology from clinically suspicious nodes, thereby obtaining International Union Against Cancer certainty factor C2. Stage I and II patients had radiotherapy alone, surgery alone, or both modalities combined. Patients with advanced disease (stage III/IV) were given combinations of surgery, radiotherapy, and chemotherapy. Pretreatment plans of all patients were discussed in a forum comprising oncologists and head and neck surgeons. The follow-up procedure was clinical examination every 2 to 3 months the first 2 years and every 3 to 4 months for the following 3 years.

Information on second primary tumors was recorded during the follow-up period and beyond. This included date of diagnosis, localization, and histology. In cases in which patients received treatment for diagnoses other than HNSCC, hospital records were obtained in all cases of new malignancies. For deceased patients, death certificates were obtained and autopsy records reviewed when available. The criteria proposed by Warren and Gates[3] were used: 1) both the first and the second tumor must be of a malignant nature, 2) they must be anatomically distinct, and 3) the second tumor should not be a metastasis of the first.

SAS software (SAS Institute, Inc., Cary, NC) was used for database records, and SPSS v.13 (SPSS, Inc., Chicago, IL) was used for data processing and statistical analysis. Three endpoints were used: death from second primary tumor, death from HNSCC, and death from any cause. Comparative survival data were analyzed according to the actuarial method.[11] The Wilcoxon test was used for univariate survival analysis. Chi-square and the Bonferroni z test method were used to test the difference in distribution between groups. P values below .05 were considered statistically significant.

TABLE I.
Patient and Tumor Characteristics.

All patients, n	2,063
Age, yrs	
Median	66
Range	21–92
Sex, n (%)	
Male	1,597 (77)
Female	466 (33)
Site of primary tumor, n (%)	
Oral cavity	796 (39)
Oropharynx	278 (13)
Hypopharynx	178 (9)
Larynx	811 (39)
Tumor classification, n (%)	
T1	575 (28)
T2	524 (25)
T3	239 (12)
T4	725 (35)
Node classification, n (%)	
N0	1336 (65)
N1	268 (13)
N2	348 (17)
N3	111 (5)

RESULTS

Patient and tumor characteristics are given in Table I. The patients included 2,063 patients in total, 1,597 (77%) males and 466 (33%) females. Age ranged from 21 to 92 years, with a median age of 66 years. Follow-up was a median of 3.3 years, and 46% of patients died of disease during the observation time. Of the four subsites, tumors of larynx (39%) and oral cavity (39%) represented the largest groups. Patients with HNSCC of the larynx had better cancer specific survival compared with other sites ($P < .05$). Oral cavity and oropharyngeal cancers showed similar survival, both better than hypopharyngeal cancers ($P < .05$) (Fig. 1).

Crude median survival among all patients was 45 months, with 5 and 10 year survival being 43% and 25%, respectively. Of all patients, 194 (9.4%) died from a second tumor.

A total of 351 of 2,063 (17%) patients developed second primary tumors. Of these, 208 (59%) were located in the upper aerodigestive tract. The mean annual rate of second primary tumors was 3.9% through the first 10 years after diagnosis of the index tumor. Forty (11%) patients were treated for local or regional recurrence before having second primary tumors.

Second primary tumors in relation to tumor and patient characteristics are shown in Table II. Risk of second malignancy was higher among patients with limited initial disease. Frequency of second primary tumors among patients with T1 and T2 tumors was 26% and 15% for T3 and T4 tumors ($P < .05$).

Of 2,063 patients, 45% had N+ disease at the time of diagnosis. The proportion of second primary tumors seen in N0 patients was 21% compared with 13%, 9%, and 6% for N1, N2, and N3 disease, respectively ($P < .05$). Incidence of second primary tumors was 19% for patients under the median age of 66 years and 15% for those older ($P = .022$).

Second primary tumors in relation to index tumor site are given in Table III. The rate was 19% for the oral cavity, 18% for the larynx, 14% for the oropharynx, and 8% for the hypopharynx ($P = .003$).

The localization of second primary tumors varied according to the primary site (Table III). The frequency of second primary tumors to the head and neck, lung, and distant organs was 32%, 21%, and 46%, respectively. Patients with the highest risk of second primary tumor had oral cavity and laryngeal index tumors. Initial disease in the oral cavity led to second primary tumors in the head and neck region in 42% of the cases ($P < .05$), whereas patients with HNSCC of the larynx had second tumors located to the lung in 24% and distant organs in 57% ($P < .05$). For hypopharyngeal and oropharyngeal index tumors, no significant association was found with second primary tumor site.

Survival after diagnosis of second primary tumor was a median of 1 year, with 5 year survival of 16%. The majority of patients (90%) died from disease.

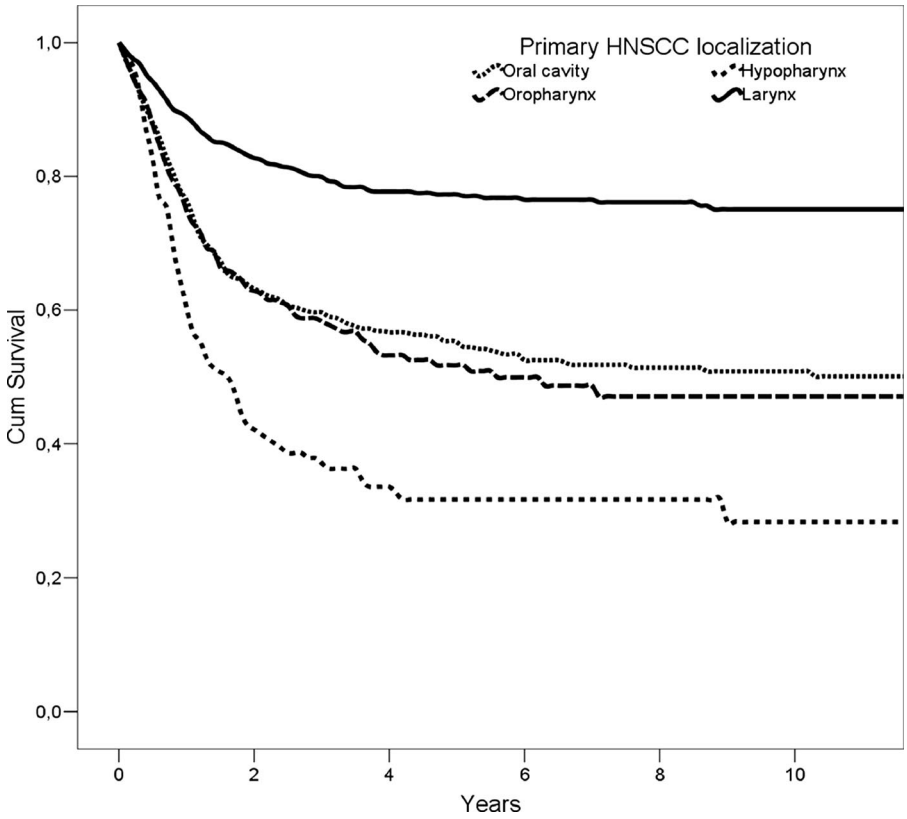

Fig. 1. Actuarial cancer specific survival for all patients (n = 2063) according to index tumor site. Five-year survival was 77% for larynx (n = 811), 54% for oral cavity (n = 796), 52% for oropharynx (n = 278) and 32% for hypopharynx (n = 178).

Figure 2 shows crude survival for patients with second primary tumors (n = 351) compared with those without (n = 1712). After diagnosis of the index tumor, survival was a median of 6 years for patients later diagnosed with second primary tumors compared with 3 years for the other patients ($P < .05$). Five-year survival was 60% for second primary tumor patients compared with 40% for patients with index tumor only. At 10 years, there was no longer a difference in survival, this being 25% in both groups.

TABLE II.
Patient and Tumor Characteristics for Patients with Second Primary Tumors.

	Second Primary	
	n	Percent
All patients	351	100
Sex		
Male	282	18
Female	69	15
Age		
Less than 66 yrs	195	19
More than 66 yrs	156	15
T-classification		
1	119	21
2	109	21
3	38	16
4	85	12
N-classification		
0	277	21
1	34	13
2	33	9
3	7	6

Cancer specific survival is shown in Figure 3. After 3 years, few patients died from primary HNSCC. The prognosis for patients developing second primary tumors was better compared with those with recurrence of index tumors, 3-year survival being 70% versus 50%, respectively. However, after 6 years, cancer specific survival was better for patients not developing second primary tumors (Fig. 3).

The rate of cancer deaths is shown in Figure 4, with survival time from the day of diagnosis of the index tumor grouped into 1 year intervals. Of patients deceased from primary HNSCC, 89% died during the first 3 years compared with 37% of patients dying from a second primary tumor.

The prognosis of second primary tumor correlated with the second tumor location (Fig. 5). No patient with a second primary to the lung survived 5 years compared with 20% of patients with a second primary located to the head and neck region or any other location. Only 13 patients had a second primary to the esophagus. All of these patients were dead 14 months after diagnosis.

DISCUSSION

The impact of second primary tumors among 2,063 patients treated for primary HNSCC over a 15 year period at our institution was investigated. In all, 351 (17%)

TABLE III.
Distribution of Second Primary Tumors According to Index Site.

	Second Primary Yes		Location of Second Primary Tumor		
	n	Percent	Head and Neck, Percent	Lung, Percent	Distant Organ, Percent
Index tumor localization					
Oral cavity	153	19	42*	16	42*
Larynx	144	18	19	24*	57
Oropharynx	39	14	28	26	46
Hypopharynx	15	8	40	20	40

*$P < .05$.

patients were diagnosed with a second primary tumor, with 194 (9%) of the patients dying from the second primary tumor. One year from the day of the second primary tumor diagnosis, half of the patients were dead.

In considering all causes of death, survival from index tumor date was better among patients developing second primary tumors compared with those who did not. Median survival was 6 years in the second primary tumor group versus 3 years for patients without new tumors. Patients who developed second primary tumors had limited primary disease, index tumor at favorable sites (larynx and oral cavity), and lower mean age.

Analysis of cancer specific survival (Fig. 3) showed that the majority of HNSCC recurrences occurred within the first 3 years, whereas second primary tumors occurred later. The interval between the index and the second tumor was found to be more than 4 years. Other studies have found this to range from 2 to 4 years,[13–14,18] which is in accordance with our findings. After 3 years, the proportion of patients dead from primary HNSCC decreased markedly, whereas the death rate related to second primary tumors remained the same (Fig. 4).

The results of this study indicate that patients with a poor prognosis did not live long enough for a second primary tumor to develop. It can be speculated that although the occurrence of a second primary tumor is a strongly negative prognostic sign, patients who develop them may represent a group with favorable initial patient and primary tumor factors, indicating higher likelihood of index tumor treatment success. Similar results were reported by Jones et al.,[13] who analyzed the records of 3,436 patients with HNSCC.

The precise mechanism behind development of second primary tumors remains to be determined. One theoretical explanation suggests that second tumors arise in condemned tissue, analogous to the "field cancerization" model.[8] Alternatively, clonal expansion may cause the spread of malignant cells from the index tumor.[15,16] In the

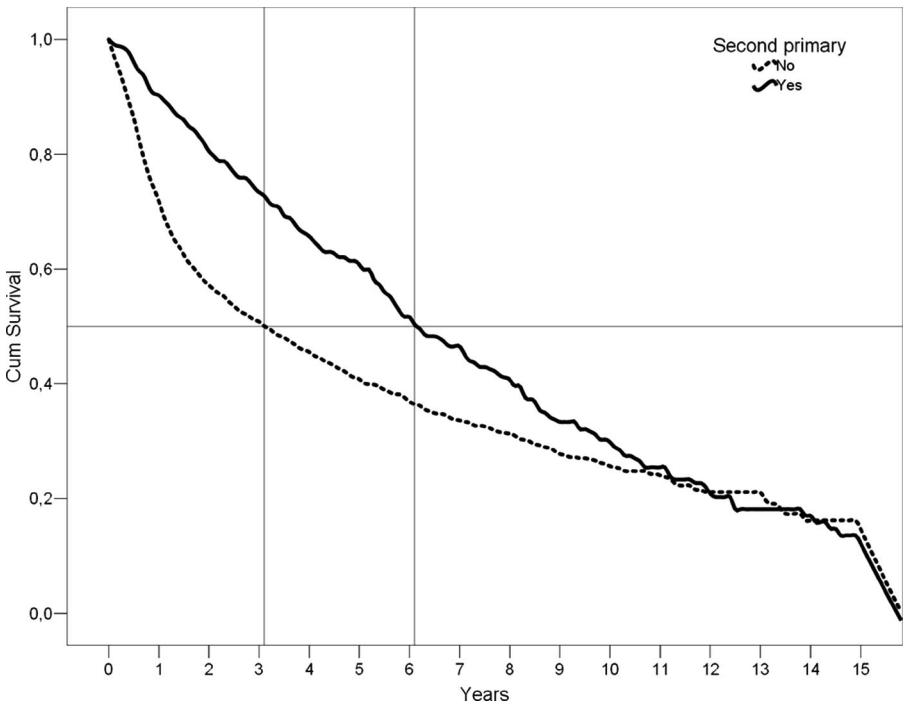

Fig. 2. Actuarial overall survival from start of index tumor treatment for patients later diagnosed with a second primary tumor (n = 351) compared to all other patients (n = 1712). Median survival time for second primary patients was 73 months vs. 37 months for patients with index tumors only ($P < 0.05$).

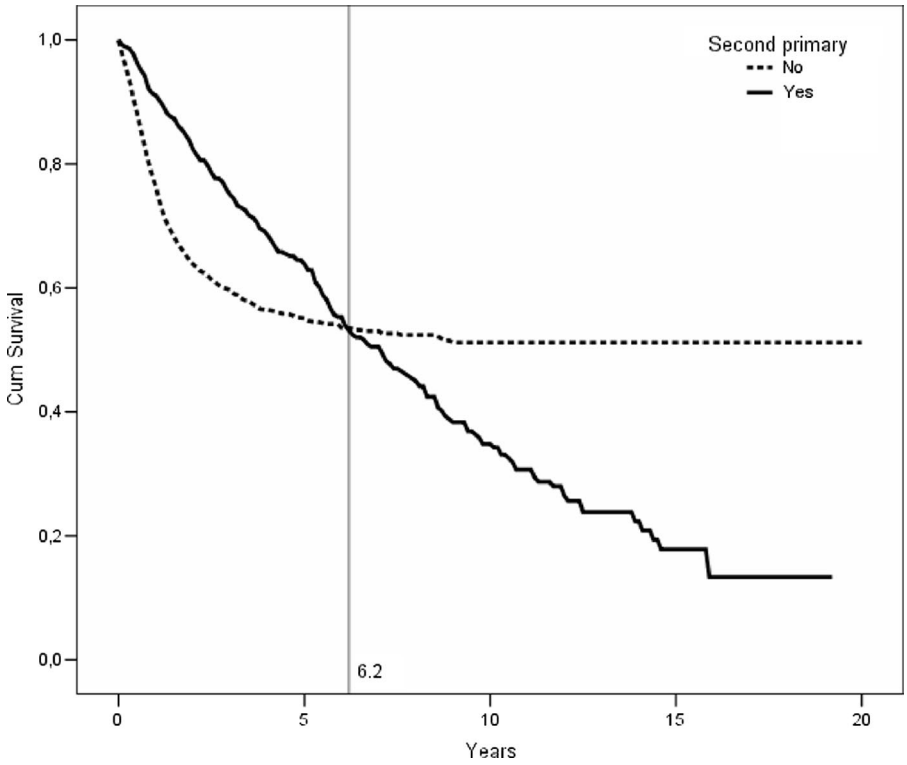

Fig. 3. Actuarial cancer specific survival from start of index tumor treatment for patients later diagnosed with a second primary tumor (n = 351) vs. all other patients (n = 1712). After 6.2 years the second primary group had worse survival.

latter case, a high number of available malignant cells from large tumors could be expected to produce more second lesions than small tumors. No such association was found, and this hypothesis cannot be substantiated by the findings in the present study and is also contradicted by other reports.[13] Whether the second primary tumors in this study were in fact second field tumors[9] could not be analyzed because no molecular biological markers were recorded in the database. Independent predictors of second primary tumor development have been shown for continued smoking and excess alcohol use.[17] Smoking habits and alcohol use were difficult to ascertain and therefore not recorded in our study.

Localization of the second tumor correlated with the site of the original index tumor because second primary tumors of the head and neck region were associated with index tumors of the oral cavity. Second primary tumors of the lung were associated with laryngeal index tumors.

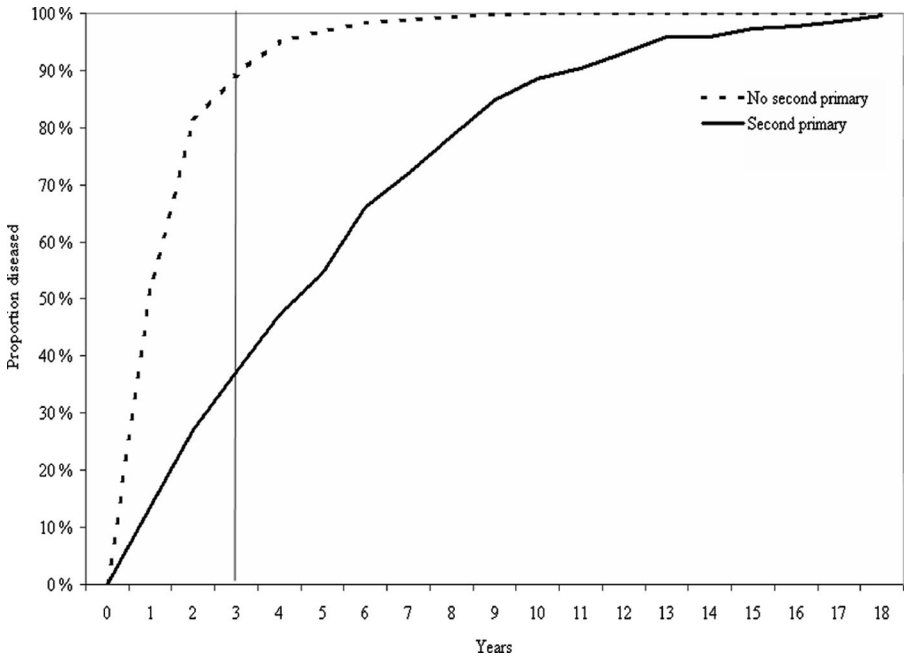

Fig. 4. Cumulative proportion of deaths from the index tumor (n = 716) vs. deaths from a second primary tumor (n = 218). Horizontal axis is years from date of diagnosis of the index tumor. After three years, 89% of deaths due to the index tumor had occurred, compared to 37% of deaths from a second primary tumor.

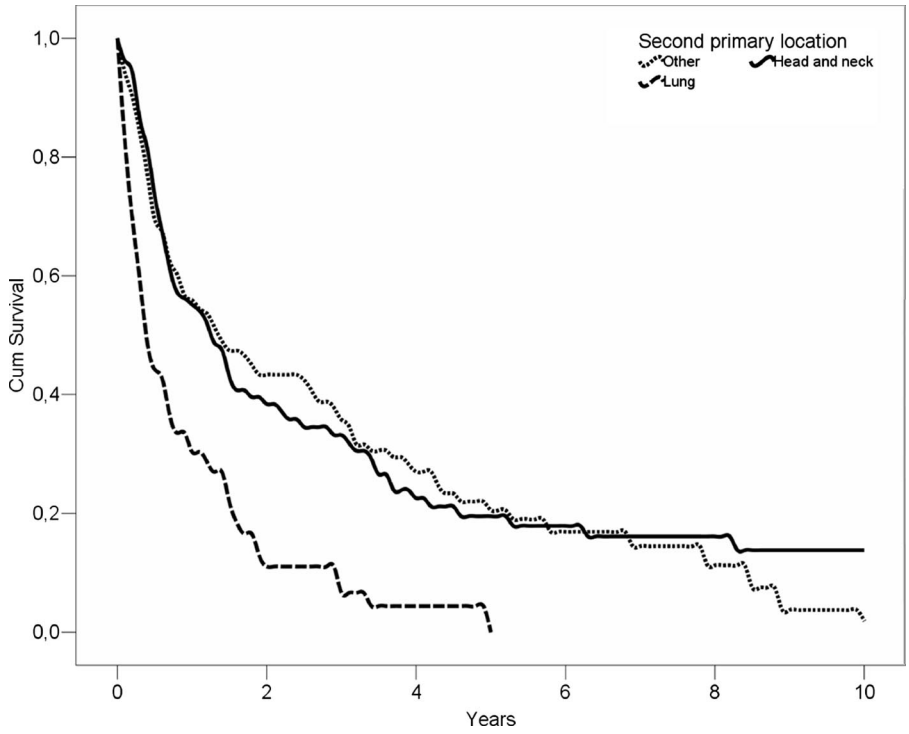

Fig. 5. Actuarial overall survival after diagnosis of a second primary vs. location of the second primary tumor. No patients with second primary to the lung survived 5 years. For second primaries located at head and neck region and in other organ systems 5-year survival is 20%.

Similar observations have been reported by other authors.[6,17–19]

The annual incidence of second primary tumors of 4% in our study concurs with previous reports.[4,5,12] The reported overall incidence varies from 8% to 27%.[4,13] The large spread of these figures probably reflects variations in observation time between different studies given the fact that annual incidence is constant.

In our study, the prognosis after second primary tumor was significantly worse when a new tumor was located in the lung as compared with other localizations. None of our patients with a second tumor to the lung survived more than 5 years, which is corroborated by previous observations.[20] The prognosis was better when second primary tumors were located in the head and neck region, a result in agreement with other reports.[5,20] The difference in survival may be explained by better treatment options for tumors of the head and neck compared with those of the lung.

CONCLUSION

In conclusion, patients at risk of developing a second primary tumor were those with less advanced tumors localized to the oral cavity and larynx. The finding of a mean 4 year delay before a second primary tumor emphasizes the need for prolonged follow-up, even in patients with good response after index tumor treatment.

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Acknowledgment of Reviewers

We would like to thank all of the people who served as reviewers for *The Laryngoscope* in 2007. The expert advice of these reviewers is essential to the peer review process.

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