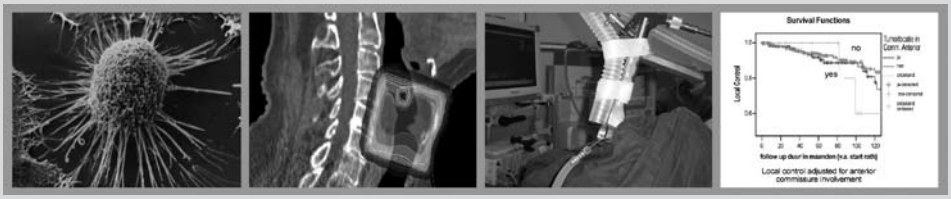
Disease outcome in T1 glottic carcinoma

Sjögren, E.V.

Chapter 4

The influence of prior tumors on survival in early (Tis-T1) glottic carcinoma

E.V. Sjögren,
S. Snijder,
S. Le Cessie,
R.J. Baatenburg de Jong



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Introduction

Early glottic carcinoma (Tis or T1) is highly curable by radiotherapy or endoscopic laser surgery yielding very high disease specific survival rates, ranging from 92 to 97% in large studies (1-4). However, other factors associated with glottic carcinoma influence overall survival in this patient group, such as multiple primary tumors and other tobacco related diseases (5). Although much attention has been paid to the effect of multiple primary (malignant) tumors on overall survival in head and neck cancer patients, the vast majority of studies focus on the effect of tumors diagnosed subsequent to the index tumor (6). However, several patients have had tumors previous to the index tumor and it is reasonable to assume that these tumors are as much part of the phenomenon of multiple primary tumors that characterize this population as the tumors subsequent to the index tumor. Therefore, patients with previous tumors may represent a high-risk population. Staging systems such as the Charlson comorbidity index (7), the Adult Comorbidity Evaluation-27 (ACE-27) (8;9) and the Washington University Head and Neck Comorbidity Index (WUHNCI) (10) already include comorbidity from other cancers. However, the relative impact of previous tumors in these indices is unclear. In addition, in retrospective analyses, scoring of all co-morbidity is difficult and may be incomplete whereas previous tumors are usually well-documented. As a prognostically significant factor, previous tumors could be more widely incorporated as a factor in clinical decision-making. The aim of this study was to investigate the occurrence of previous tumors and the magnitude of their impact on survival in patients with early glottic carcinoma, a patient population in which the disease itself has a relatively minor effect on overall survival.

Patients and methods

This study was conducted in the region of the Comprehensive Cancer Centre West. The registry covers 1.6 million inhabitants, which equals 10% of the population of the Netherlands. Four oncological centers serve this district.
All patients diagnosed with early glottic carcinoma within the Comprehensive Cancer Centre West region between 1982 and 1993 were included in this study, making it population based. The cut-off date for the follow-up was December 31, 1999. Demographic data are shown in table 1.

Patient data, data on the index (glottic) tumor and on tumors previous or subsequent to the index tumor were collected by review of patient charts and matched with hospital and regional cancer registries. Basal cell and squamous cell carcinomas of the skin were not included in the database. In this study, we chose not to use the term *second malignant tumors* because for patients with previous tumors a tumor subsequent to their T1 glottic carcinoma would be their third tumor. We therefore use the term *multiple primary tumors*. Multiple primary tumors were divided in tumors either previous or subsequent to the

Table 1 | Patient characteristics.

Characteristic	n
age (years)	
mean	65
range	37-91
gender (male: female)	321:38
T-stage (Tis: T1)	40:319
follow-up (months)	
mean follow up	91
range follow-up	1-204
patients lost to follow-up	18 (5%)
mean follow-up of patients lost to follow-up (months)	36

glottic tumor. Follow-up was calculated in months from the date of diagnosis of the glottic carcinoma to the last follow-up examination or the cut of date in cases in which the last examination occurred after this time. Patients with less than 5 years of follow-up were considered lost to follow-up. The cause of death was obtained from the cancer registry records supported by careful examination of the clinical records.
Survival probabilities (overall survival, local recurrence and disease specific survival) were calculated using the Kaplan-Meier method starting from the date of diagnosis of the glottic carcinoma.
The effect of all previous tumors overall survival was tested in univariate (log-rank) and multivariate analysis (Cox regression) together with the variables: gender, age, tumor stage, non-malignant comorbidity, smoking habit and subsequent tumors. The analysis was also repeated including only tumors diagnosed more than 6 months before the index tumor in the previous tumor category. This was to investigate whether any effect would be due only to newly diagnosed previous tumors. Subsequent tumors were entered as a time-dependent variable in multivariate analysis. Age was divided into 4 groups. Tumor stage was Tis or T1. One hundred and sixty cases of non-malignant comorbidity were recorded in 141 patients (table 2).

As not enough data on severity and duration of the various comorbidities was available to use one of the existing classifications (Charlson or ACE-27) it was only entered as present or not present in analysis, without assigning weight to the type or severity of the individual diseases. Patients were classified as smokers or non-smokers, with patients who had never smoked or who had stopped more than 10 years earlier being classified as non-smokers. As we had 17 missing values for this variable and as it was not significant in univariate analysis it was left out of multivariate analysis.

Table 2 | Number and Types of Comorbidity.

Comorbidity type	Number of patients
none recorded	218
COPD	28
lung fibrosis	2
peripheral vascular disease	20
cerebral infarction	10
myocardial infarction	32
heart failure	3
cardiomyopathy	5
cardiac valve disease	4
hypertension	18
stomach ulcer	10
stomach resection	3
liver disease	6
renal disease	1
dementia	1
epilepsy	1
connective tissue disease	2
diabetes	6
hyperthyroidism	3
tuberculosis	5

Abbreviation: COPD, chronic obstructive pulmonary disease

Results

One-hundred and eleven of 359 patients (31%) had multiple primary tumors. Eighty-nine patients (26%) developed a total of 105 tumors subsequent to the glottic carcinoma (table 3) of which 98 were first subsequent tumors and 7 were second subsequent tumors.

Twenty-two patients (6%) had a total of 23 previous tumors (table 4). Of the previous tumors, 16 (70%) were smoking related tumors (lung, bladder). The median time between diagnosis of the previous tumor and the glottic carcinoma was 63 months, ranging from 1 week tot 172 months. Eighteen of the 23 previous tumors occurred more than 6 months before the index tumor. One patient had a previous tumor recorded in her hospital chart without a date of diagnosis. This tumor was not found in the cancer registry. Probably it had occurred before the cancer registry was established in 1986. Five patients died due to their previous tumor and 7 patients died due to other causes. Only 12 patients died of their glottic carcinoma. For two patients there was not enough information in the charts and cancer registry to accurately determine the cause of death. Eighteen patients (5%) had less than 5 years of follow-up and were considered lost to follow-up.

Table 3 | Localization and number of subsequent tumors.

Localization of tumors	Number of tumors	Incidence (%)
UAD		
lung	40	11.1
ENT	6	1.7
esophagus	1	0.3
Other tobaccor related		
bladder	9	2.5
pancreas	5	1.3
Other		
nose/sinus	1	0.3
stomach	1	0.3
colon	8	2.5
rectum/anus	9	2.2
liver	2	0.6
bone marrow	2	0.6
breast	1	0.3
breast male	1	0.3
uterus		0.3
prostate	11	3.1
kidney	4	1.1
eye	1	0.3
lymph node	1	0.3
unknown primary	2	0.6
Total	**105**	

Abbreviations: UAD, upper aerodigestive tract; ENT, ear, nose and throat

The 5- and 10-year overall survival for the entire study population was 78% and 60%, respectively. The results of univariate analysis for overall survival are shown in table 5. In univariate analysis previous tumors (all) ($p<0.0002$), age ($p<0.06$), subsequent tumors ($p<0.0001$), and non-malignant comorbidity ($p=0.002$) had a significant impact on survival. Previous tumors (more than 6 months before index tumor) were of borderline significance age ($p<0.06$).

In multivariate analysis (table 6) previous tumors retained their negative impact on survival, both when all previous tumors (relative risk [RR] 3.4, $p<0.001$) and only previous tumors diagnosed more than 6 months before the index tumor (RR 2.6, $p=0.01$) were

Table 4 | Characteristics of previous tumors.

Localization	Time before index tumor (months)	FU (months)	Status at last FU	Cause of death
lung	1 week	1	dead	lung cancer
lung	2 weeks	7	dead	lung cancer
lung	3 weeks	39	dead	lung cancer
lung	5	12	dead	metastatic lung cancer
lung	66	10	dead	cerebrovascular accident
lung	121	147	alive	alive
lung	124	9	dead	unknown
lung	172	84	dead	hart failure
lung	49	4	alive; lost to FU	alive
bladder	?	43	alive; lost to FU	alive
bladder	3	105	dead	metastases bladder
bladder	25	105	alive	alive
bladder	46	85	alive	alive
bladder	83	95	alive	alive
bladder	89	66	alive	alive
prostate	28	139	alive	alive
prostate	132	96	alive	alive
testis	143	8	dead	regional recurrence larynx
colorectal	47	8	dead	unknown
colorectal	81	22	dead	unknown although no recurrent tumor
colorectal	83	65	dead	unknown although no recurrent tumor
colorectal *	108	29	dead	unknown although no recurrent tumor

Abbreviations: FU, follow-up * same patient

considered. Further factors, with an independent impact on overall survival in multivariate analysis were subsequent tumors and age. Non-malignant comorbidity had no significant impact on survival although a slight change in the p-value occurred when only previous tumors diagnosed more than 6 months before the index tumor were considered, shifting comorbidity into borderline significance. We do not consider this to imply a clinical difference between the two groups of previous tumors.

Table 5 | Univariate analysis for 5-year rate of overall survival.

Factor	Number of patients	5-year overall survival	p-value
age (years)			
< 60	111	91%	
60-69	115	84%	
70-79	101	66%	
≥ 80 years	32	44%	<0.0001
gender			
male	319	77%	
female	38	84%	0.51
tumor stage			
T1	319	76%	
Tis	40	78%	0.86
previous tumor (all)			
yes	22	6%	
no	337	94%	0.0002
previous tumor (>6 months before index tumor)			
yes	17	5%	
no	342	95%	0.06
subsequent tumor			
yes	89	25%	
no	270	75%	<0.0001
nonmalignant comorbidity			
yes	112	69%	
no	247	81%	0.002
smoking			
yes	260	77%	
no	82	79%	0.28

Previous tumors had no effect on the rate of loco-regional recurrence or disease free survival. At 5-years the recurrence free survival was 92% for patients without a previous tumor and 95% for patients with a previous tumor (p=0.40). For disease free survival it was 97% and 95% (p=0.65).

Table 6 | Multivariate analysis (Cox regression) for 5-year overall survival.

	Overall survival all previous tumors			previous tumors diagnosed > 6 months before index tumor		
Factor	HR	95% CI for HR	p value	HR	95% CI for HR	p value
age*						
< 60 years						
60-69 years	1.4	0.9 - 2.6	0.10 [y]	1.5	0.9 - 2.6	0.10 [y]
70-79 years	2.8	1.7 - 4.8	<0.0001 [y]	3.0	1.8 - 4.9	<0.0001 [y]
≥ 80 years	7.4	4.1 - 13.7	<0.0001 [y]	7.3	3.4 - 13.4	<0.0001 [y]
subsequent tumors	9.2	6.2 - 13.6	<0.0001 [y]	9.0	6.1 - 13.2	<0.0001 [y]
previous tumors	3.4	1.8 - 6.3	<0.001 [y]	2.6	1.2 - 5.5	0.01 [y]
non-malignant comorbidity	1.3	0.9 - 1.8	0.15	1.4	1.0 - 2.0	0.06
gender	1.3	0.7 - 2.6	0.39	1.4	0.7 - 2.6	0.35
tumor stage	1.0	0.6 - 1.7	0.94	1.0	0.6 - 1.8	0.98

Abbreviations: CI, confidence interval; HR, hazard ratio
* HR is shown in relation to the <60 years age group
[y] significant

Discussion

A lot of attention has been paid in the literature to the phenomenon of multiple primary tumors subsequent to head and neck carcinomas and their influence on survival. However, previous tumors that are also part of this phenomenon are usually not considered in prognostication or medical decision-making, which is still largely based on adherence to the TNM staging system. In this study we were particularly interested in determining the effect of previous tumors on overall survival in patients with early glottic carcinoma, especially because of the high disease specific survival in this patient population.

Several validated instruments, such as the Charlson index, ACE-27and the WUHNCI (7-10), among others, already exist to measure and classify the overall severity of comorbidity, including previous tumors. However, because most studies, including this one, are carried out retrospectively, it is difficult to obtain information on comorbid disease that is adequate and detailed enough for the retrospective use of these instruments. In this study, we therefore chose to classify non-malignant comorbidity simply as present or not present, without assigning weight to the type or severity of the individual diseases.

The 5- and 10 year overall survival rates in our patient group of 78% and 60% were in accordance with literature (11;12). Nearly one-third of all patients with early glottic cancer suffered from multiple primary tumors: 6% had previous tumors, of which 70% were defined as smoking related (lung, bladder). We found previous tumors to be associated

with a significant decrease in overall survival (RR 3.4, p<0.001) independent of age, subsequent tumors, tumor-stage, gender and non-malignant comorbidity. This effect remained, although weaker, when only previous tumors diagnosed more than 6 months before the index tumor were considered (RR 2.6, p=0.14). This supports the intuitive notion that the time-span between the previous tumor and the glottic carcinoma (index) tumor plays a role in the impact on survival. It means that patients, who have survived their previous tumor for a longer period of time, have a better prognosis than patients in which the previous tumor has more recently been diagnosed. The ACE-27 and the WUHNCI but not the Charlson Comorbidity Index, recognizes this by distinguishing between newly diagnosed and older tumors. Further quantification of the effect of different morphologies of previous tumors and the time span between them and the index tumor is possible and several new methods are currently being developed for this purpose (13). Not surprisingly, other factors with an influence on survival were subsequent tumors and age. Although subsequent tumors cannot be used for prognostication at the time of diagnosis, it is important to realize that even if Tis-T1 glottic carcinoma has excellent rates of disease specific survival, patients are at an increased risk of developing further tumors compared to the general population and that this, in turn, influences survival (14-16). In this study, 25% of patients developed additional tumors which increased their risk of dying nine-fold. Non-malignant comorbidity was only of borderline significance. Several studies have shown that head and neck cancer patients with comorbidity have a worse outcome than patients without comorbid disease (6;17;18;19). However, these studies group localizations and T-stages in analysis. Because early glottic carcinoma is a relatively mild disease and because treatment is relatively undemanding, it is tolerated better than treatment for other types of head and neck cancer. Therefore, there may be less impact of comorbidity on overall survival in these patients than has been shown in other forms of head and neck cancer. Also, a recent study comparing seven different validated comorbitiy rating scales in patients with surgically treated laryngeal cancer showed that all comorbidity scales were able to predict survival in univariate analysis, but only the Cumulative Illness Rating Scale (CIRS) was able to do so in multivariate analysis (20;21). This means that there is also some variation in results depending on which index is chosen. On the other hand, as this is a retrospective study, registration of comorbidity in patients' charts may have been insufficient.

Two patients with a previous tumor had less than 5 years of follow-up. However, should these patients have died shortly after the loss this would only have strengthened the observed effect. When analysis was repeated, assuming they would have been withdrawn alive at the end of the study, there was no change in the results of multivariate analysis (data not shown). Therefore, we believe that this small loss to follow-up at the worst diluted the effect of previous tumors on survival.

Conclusion

These results show that previous tumors occur in a group (6%) of patients with early glottic carcinoma and they have an independent impact on overall survival in this patient group. In this study patients with early glottic carcinoma and a previous tumor as a group had 3.4 times the risk of dying during our follow-up compared to patients without a previous tumor. This risk was time-related and decreased to 2.6 times if the tumor was diagnosed more than 6 months before the glottic tumor. The effect of previous tumors was stronger than that of other (nonmalignant) comorbidity which was only of borderline significance. These findings show that although disease-specific survival is very high in early glottic carcinoma, overall survival is limited in patients with previous tumors. This supports the concept of incorporating data on previous malignancies (and other comorbidity) into the existing TNM tumor staging system to improve the accuracy of prognostication and to aid in treatment decisions for the individual patient.

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