

Secondary oesophageal or gastric cancer in patients treated for head and neck squamous cell carcinoma

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ABSTRACT

INTRODUCTION: Patients with head and neck squamous cell carcinoma (HNSCC) are at an elevated risk of developing second primary malignancies (SPM). Our objectives were to estimate the excess risk of oesophageal and gastric SPMs in patients with malignancies of the pharynx or larynx and, additionally, to examine possible risk factors of developing SPMs.

METHODS: Data on all patients treated for HNSCC with curative intent in the Region of Southern Denmark in the period between 1 January 2000 and 31 December 2010 were reviewed. A total of 1,172 patients were identified. The combined data from the DAHANCA database, the Danish National Pathology Registry and the patient charts were analysed.

RESULTS: A total of 27 patients developed a SPM in the oesophagus or stomach corresponding to a standardised incidence ratio of 9.5 (95% confidence interval (CI): 6.5-13.9). Supraglottic (odds ratio (OR) = 6.9; $p < 0.004$) and hypopharyngeal (OR = 3.9; $p < 0.049$) index tumour sites were significant risk factors for developing SPM. The median survival of patients with SPM was 3.6 years (95% CI: 1.6-5.1; range: 0.7-12.4) from diagnosis of the index cancer compared with 3.4 years (95% CI: 3.1-4.3; range: 0.04-13.7) for patients without SPM.

CONCLUSION: In this study, we confirm that there is an elevated risk of developing oesophageal and gastric cancer in the Danish population of patients with a cancer in the supraglottic or hypopharyngeal region. Therefore, we recommend close follow-up of these patients and a low threshold for examination of the oesophagus and stomach.

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Several studies have shown an excess risk of second primary malignancies (SPMs) among patients with head and neck squamous cell carcinomas (HNSCCs). It is postulated that this is an important factor in explaining why these patients' survival has not increased despite improvement in the treatment modalities [1, 2]. The anatomic sites with elevated risk of SPM seem to be the head and neck, lungs and oesophagus. Diagnosing SPMs in the oesophagus is challenging as the symptoms mimic the side effects typically seen following radiation therapy of malignancies in the head and neck region. There-

fore, SPMs of the oesophagus are rarely detected at an early stage despite intensive surveillance of these patients.

It remains uncertain to what extent the combination of HNSCCs and oesophageal/gastric cancers is prevalent in the Danish population and how it affects survival. The overall five-year survival rate for patients with cancer of the pharynx and larynx is 25-50% and 62%, respectively, compared with 11% for patients diagnosed with oesophageal cancer [3]. The presumed survival of the patients developing SPMs is lower, and recognition of these tumours at an early stage is likely to be of great importance for the prognosis [4, 5]. The risk factors for developing SPM are not clarified, but age, gender, alcohol ingestion and anatomic site of the index cancer seem to be of importance [6, 7]. The aim of this study was to clarify the frequency of second primary oesophageal and gastric cancers in patients with malignancies of the pharynx and larynx who have undergone treatment with curative intent in a geographically well-defined cohort. Furthermore, patient characteristics with possible influence on the risk of developing SPM, as well as tumour type and TNM stage of the SPMs, were examined.

METHODS

Data on all patients treated for HNSCC with curative intent in the Region of Southern Denmark in the period between 1 January 2000 and 31 December 2010 were extracted from the Danish Head and Neck Cancer Group (DAHANCA) database. Patient characteristics, co-morbidity and tumour stage have been registered consecutively in the DAHANCA database since 1970, and this registration has been fully established nationwide since 1991. The database correlates 96% with the Danish Cancer Registry, which aims to register all cancer cases in Denmark [8, 9].

To identify the patients with SPMs in the oesophagus or stomach, the DAHANCA data were matched with data from the Danish National Pathology Registry (PATOBANK), which is a national database containing data from all pathology reports in Denmark. Second cancers include both synchronous (diagnosed within six months from HNSCC diagnosis) and metachronous oesophageal and gastric cancers. This study does not dif-

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ferentiate between synchronous and metachronous SPMs. Thus, all patients with a Systematized Nomenclature of Medicine (SNOMED) code representing oesophageal or gastric topography as well as malignancy in the PATOBANK were matched with the DAHANCA database using the patient's social security number. All malignancies registered between 1 January 2000 and 31 October 2013 were included. With this approach, only the histologically verified malignancies were examined, and patients who had moved to another region of Denmark were not lost during follow-up.

Patients in the study group underwent examination according to the national DAHANCA guidelines in which gastroscopy is not a routine procedure in suspected laryngeal or pharyngeal cancer [10].

The information about diagnosis, co-morbidity, risk factors, TNM stage, treatment strategy, etc. was obtained from the DAHANCA database and supplemented through patient chart reviews. Symptoms of SPMs were also registered.

When calculating the incidence, the crude rate in the study population was not comparable with that of the general population because of the difference in distribution of age and gender in the two populations. Therefore, the standardised incidence ratio (SIR) was used. SIR was defined as the ratio between the observed and the expected number of patients with oesophageal and gastric cancer. The expected number was obtained by applying the age- and sex-specific incidence rates in Southern Denmark to the study population. The age- and gender-specific incidence rates were obtained from The Association of the Nordic Cancer Registries (ANCR), which unifies data from the Nordic national cancer registries [11, 12]. To match the study period, the incidence rates from 2000 to 2011 were used. The risk time, the

number of person years at risk (PYR), in the patient groups was defined as the number of years from the date of the diagnosis of an index cancer to either the date of diagnosis of SPM, the date of death or the end of the study period.

To compare the risk factors, a control group was picked randomly from the patients not diagnosed with oesophageal or gastric cancer with a ratio of four controls to one case.

Trial registration: not relevant.

Statistics

Data were recorded and analysed in STATA 13. 95% confidence intervals (CIs) were calculated for the SIRs. Univariate logistic regression (reporting ORs) and multivariate logistic regression were performed to evaluate each risk factor. Survival was estimated by the Kaplan-Meier method including log-rank test for comparison of survival. For group comparison of the risk factors, we used the Cox proportional hazards model (hazard ratios with CIs). $p < 0.05$ was considered statistically significant.

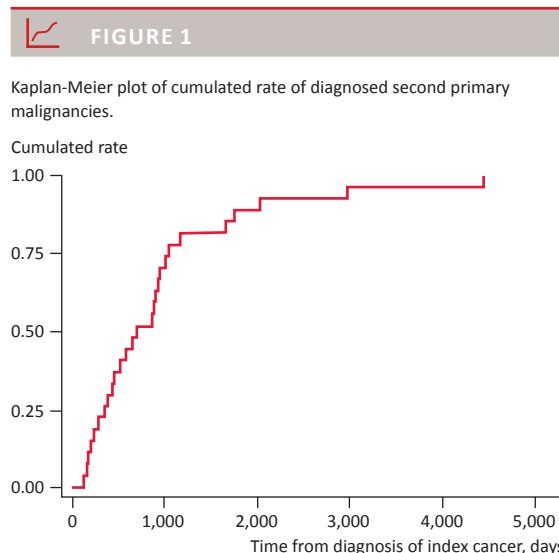
RESULTS

A total of 1,172 HNSCC patients were identified, and 27 (2.3%) patients had an SPM. The SPM was diagnosed at a median age of 63.2 years (95% CI: 58.9-67.8; range: 53.2-81.9) and with a median time interval of 23.0 months (95% CI: 14.3-31.1; range: 4.0-146.0) after the diagnosis of the HNSCC. The cumulated rate of diagnosed SPMs is seen in **Figure 1**.

The combined data from the DAHANCA database and the PATOBANK identified four patient categories: 1) oesophageal or gastric cancer as the second cancer, 2) oesophageal or gastric cancer as the index cancer, 3) HNSCC involving part of the oesophagus and 4) patients who underwent biopsy of the oesophagus with normal histology who simultaneously underwent biopsy of another location (i.e. the larynx or pharynx) with histologically confirmed malignancy. Review of the patient charts of the latter group of patients showed no clinical signs of oesophageal cancer and they were therefore excluded. Only the patients from the first group were included in this study.

Symptoms, diagnosis and treatment of second primary malignancies

A large number of the patients developing SPM experienced persistent, increasing or new-onset dysphagia, haematemesis, epigastric pain or painful swallowing during the period from completing radiotherapy to the diagnosis of the SPM. Of these 27 patients, 17 (63%) had consulted a doctor > 2 months before the SPM was diagnosed as they experienced at least one of the symp-



toms. Of these, seven were seen by the doctor > 6 months before the SPM was diagnosed. During this period, oesophagoscopy was performed in eight of the 17 patients; and in four patients, a narrowing of the oesophagus was recognised at the tumour site, but initially considered to be benign.

In the population studied, curative treatment of the SPM was initiated in five (18.5%) patients while the majority had no or only palliative treatment. Tumour characteristics of the SPMs are shown in **Table 1**. Few patients were candidates for therapy and many did not complete the full examination programme. Therefore, the registration of TNM stage of the SPM in the patient charts was incomplete in several cases. The anatomic location of the SPM was the proximal third in six (22.2%) patients, the middle third in five (18.5%) patients and the distal third of the oesophagus in ten (37.0%) patients, while six (22.2%) of the SPMs were located to the stomach.

Standardised incidence ratio for second primary malignancies

The ratio of oesophageal and gastric cancer not adjusted for age, gender or time at risk was 2.3%. The 27 SPMs were observed over 5,610 PYR. Using the age- and gender-specific incidence rates, calculated with data from ANCR, the expected number of SPMs would be 2.8 [12]. Therefore, the SIR for oesophageal and gastric cancer was 9.5 (95% CI: 6.5-13.9) compared with the general population of the Region of Southern Denmark.

Risk factors for developing second primary malignancies

Patient demographics and risk factors (gender, age at HNSCC diagnosis, body mass index at HNSCC diagnosis, smoking status, index tumour site, Union for International Cancer Control (UICC, 2010) stage and TNM stage of the index cancer) were initially analysed by univariate analysis. The site of the index tumour had a significant influence on the development of SPM. The patients with supraglottic index tumours had the highest risk of SPM compared with index tumours located in the oropharynx (OR = 6.9; $p < 0.004$). In addition, patients with hypopharyngeal index tumours were at increased risk (OR = 3.9; $p < 0.049$) of developing a SPM. However, a multivariate analysis did not reveal any different significant results.

Survival analysis

The median survival was 3.6 years (95% CI: 1.6-5.1; range: 0.7-12.4) for patients developing a SPM and 3.4 years (95% CI: 3.1-4.3; range: 0.04-13.7) for patients not developing SPM. When comparing the two median values, we found no statistically significant difference.



TABLE 1

Tumour characteristics of the second primary malignancies.

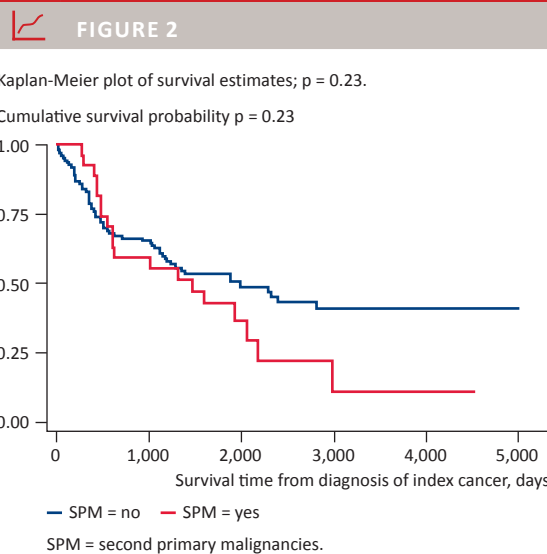
	Frequency	%
<i>T-stage</i>		
1	3	11.1
2	4	14.8
3	7	25.9
4	1	3.7
No data	12	44.4
<i>N-stage</i>		
0	7	25.9
1	9	33.3
No data	11	40.7
<i>M-stage</i>		
0	15	55.6
1	4	14.8
No data	8	29.6
<i>Treatment</i>		
None	10	37.0
Palliative therapy	11	40.7
Chemotherapy with curative intent	5	18.5
Other	1	3.7
<i>Age at diagnosis, yrs</i>		
50-60	11	40.7
60-70	11	40.7
> 70	5	18.5
<i>Cancer site</i>		
Proximal 3rd	6	22.2
Middle 3rd	5	18.5
Distal 3rd	10	37.0
Cardia and stomach	6	22.2
<i>Histology</i>		
Squamous cell carcinoma	18	69.2
Adenocarcinoma	8	30.8

Median survival from diagnosis of SPM was 5.0 months (95% CI: 0.7-10.3; range: 0.0-41.1). The survival curves for patients with and without SPM are shown in **Figure 2**. When analysing the factors with impact on the survival of the patients; weight (hazard ratio (HR) = 0.98; 95% CI: 0.96-0.99; $p < 0.009$), age at diagnosis (HR = 1.02; 95% CI: 1.00-1.05; $p < 0.050$), and N-stage of the index cancer (HR = 1.38; 95% CI: 1.09-1.75; $p < 0.008$) were identified as significant predictors of survival.

DISCUSSION

This case-control and retrospective cohort study based on the population of Southern Denmark confirmed an increased risk of developing oesophageal or gastric cancer following HNSCC, supporting the theory of an association between these cancer types.

Surprisingly, the odds for developing oesophageal or gastric cancer among patients with an index cancer located in the supraglottic part of larynx were significantly higher than in patients with an index cancer lo-



cated in the oropharynx. Previous studies found that tumours tend to follow either a respiratory (larynx-lung) or digestive (pharynx-oesophagus) axis [1, 6, 13]. This divergence could possibly be explained by the increasing number of human papillomavirus (HPV)-associated oropharyngeal malignancies in the past decade. For the period from 1975 to 2006, Morris et al [14] found that the risk of SPM of the oesophagus significantly decreased in patients with oropharyngeal cancer, but increased in patients with cancer in the larynx, although this was not statistically significant. Unfortunately, in our study it was not possible to analyse how the HPV influences the risk of SPM, since HPV status registration in the DAHANCA database only started recently. However, a recent study of the impact of index HNSCC tumour site on SPM risk [15] found that patients with an index HNSCC of the oropharynx and a typical HPV phenotype had a very low SPM rate.

We found no significant difference in survival between patients with and without SPM. This may be due to the overall excess mortality among head and neck cancer patients [16] and the fact that the non-SPM group had several competing causes of death [17], e.g. HNSCC, SPM of the lung and cardiovascular disease. Recent studies show a six-fold higher overall mortality risk in patients with cancer of the oral cavity and oropharynx compared with the general population, mainly due to alcohol- and tobacco-associated diseases [18]. However, we found no significant difference between the two groups in the distribution of the analysed risk factors. Another explanation may be that patients developing SPMs have to survive long enough for the SPM to develop, which would mean that SPM may be an indirect positive prognostic factor [19]. In the present study,

the median interval from diagnosis of the index cancer to diagnosis of the SPM was 23 months, partly supporting this hypothesis.

This study has some limitations. The retrospective design forced us to rely on the accuracy of the databases, and the possibility that some SPMs were misclassified as metastases or recurrences exists, particularly for malignancies in the upper third of the oesophagus. We aimed to minimise this by reviewing the charts of all patients who underwent biopsy of the oesophagus simultaneously with having a tumour classified as HNSCC. Besides misclassification, it is possible that we underestimated the number of patients developing a SPM as some patients may have died before the biopsy or even before recognition of the oesophageal or gastric cancer. Furthermore, it is noteworthy that the patients who were diagnosed with HNSCC in the late phase of the study (2010) were followed for less than three years and therefore just exceeded the mean time from diagnosis of the index cancer to diagnosis of the SPM possibly leading to further underestimation of SPMs. Ideally, the study should have had an even longer follow-up time. The strengths of the study, on the other hand, are the inclusion of all patients treated in the Region of Southern Denmark, which is an area that is representative of the whole Danish population, the high quality control of the DAHANCA database, the completeness of the PATOBANK database and the completeness of the follow-up data.

CONCLUSION

Based on a geographically well-defined cohort from the Danish population our study confirms that patients with an HNSCC are at an elevated risk of developing oesophageal and gastric cancer, and it shows that these second primary tumours represent a threat to the patients who survive the HNSCC. Our data and several published studies support that this excess risk justifies close follow-up of these patients and a low threshold for examination of the oesophagus and stomach.

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