Proximal Esophageal Cancer: Prevalence of previous tumors and their influence on survival

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ABSTRACT
Proximal esophageal cancer (PEC) is a highly mortal cancer with a five-year survival rate of 30%. Because second primary tumors could decrease survival in PEC patients, this research is aiming at finding out about tumors associated with PEC and their infuence on survival. With the use of a database with PEC patients, diagnosed between 1989 and 2014, it was found that head and neck cancers (H&N) are the most prevalent previous tumor in PEC patients. Previous tumors have a negative effect on surivval. Prospective studies are needed to investigate on the effectiveness of prevention and surveillance methods for H&N patients.

Keywords
proximal esophageal cancer, previous tumors, survival

INTRODUCTION

The proximal esophagus is located between the inferior border of the cricoid cartilage and the carina, up to 24 cm from the incisor teeth. A special part of the proximal esophagus is the cervical esophagus, which extents 18 cm from the incisor teeth. Tumors of the cervical esophagus, which is the most complex part of the proximal esophagus, is an uncommon disease accounting for around 2 to 10% of all esophageal cancers (EC) (1). Its complexity originates from the fact that is located between the thoracic inlet and the inferior border of the cricoid cartilage with proximity to adjacent structures like the thyroid gland, thyroid cartilage and cricoid. Histology of this cancer is squamous cell carcinoma (SCC) in 95% of the cases (2).
Esophageal squamous cell carcinoma (ESCC) in general and cancer of the proximal esophagus (PEC) in specific have shown to be associated with cancer of the lung, head and neck (H&N), which was shown is prior studies The incidence of ESCC in H&N cancer is 12.4% according to a study by Laohawiiyakamol et al. (13).. ESCC is associated with colorectal cancer and with cancers of the oral cavity, the pharynx, larynx, the lung, kidney, thyroid and bladder (14, 15). Furthermore, studies have shown that second primary tumors in patients with H&N tumors can influence survival of cancer patients, as survival is lower in patients who have a H&N subsequent cancer compared to no cancer at all (16). Lee et al. has shown that survival is decreased in a patient group of ESCC when patients present with a synchronous malignancy (17). The development of second primary tumors (SPT) is enhanced by shared risk factors of PEC and tumors of the upper aerodigestive tract (UADT), like tobacco smoking and alcohol abuse (19). The effect of these risk factors is enhanced when the esophagus suffers mechanical damage, which can be case in achalasia or a consequence of administration of sodium hydroxide (20, 21).
The presence of other tumors in a locally related area is often explained by the term “field cancerization”. The core concept of this theory is that there is an area adjacent to the tumor which shows some pre-malignant genetic mutations and therefore is of high risk of becoming entirely malignant, which can be enhanced by the previously mentioned risk factors alcohol and tobacco consumption (7).
Irradiation by e.g. radiotherapy can also be an important inducer of second primary cancer, as the radiation causes DNA damage and increase the probability of these cells to become malignant. There is evidence that therapeutic radiation of H&N cancer can cause ESCC via damage of the DNA and therefore increase the potential of cells turning into malignancies (22).
Zhang et al. and Hashibe et al. have shown has shown that irradiation can cause the formation of SPT, with a development interval of more than 10 years (3, 4).
In contrast, second primary cancers which have developed as a result of smoking tobacco develop earlier after exposure. Because of this temporal relationship it is possible to link the respective risk factor – smoking and alcohol or radiation – to the tumor and estimate which one of the two risk factors might have caused the SPT.
Knowledge about PEC associated tumors, who could probably be caused by the previous mentioned risk factors could be used to prevent the development of PEC by avoidance of the known risk factors in the first place and screening of the (upper) esophageal tract in the second place.
In order to ultimately increase survival of patients with PEC, it is required not only to focus on the main malignancy, but also explore the associated other previous tumors a patient with PEC might suffer from. The aim of this research is to explore patients which present with PEC and a previous other tumor by analyzing data of patients with cancer of the proximal esophagus diagnosed between 1989 and 2014 by the Netherlands Comprehensive Cancer Organization (IKNL).
The present research will investigate on PEC, including tumors of the cervical esophagus (classified as location C15.0) and the upper third of the esophagus, extending from the thoracic inlet to the level of the tracheal bifurcation, approximately 24 cm from the upper incisor teeth (classified as location C15.3). With this retrospective study, we will investigate on the prevalence of previous tumors in patients with PEC and the influence of those associated tumors on the survival as a primary outcome. The hypothesis is that patients with PEC will have a high prevalence of tumors of the aerodigestive tract, meaning H&N, ESCC and lung cancers and that these occur only a short time interval before the diagnosis of PEC, suggesting a more prominent role of risk factors in the evolution of a second tumor, and a limited role for treatment-induced influence on the development of the PEC. In addition, we hypothesize that the survival of patients with PEC is lower in patients who have already suffered from another primary tumor, due to morbidity after the previous treatments, and possible constraints in treatment options for PEC, e.g. after extended radiotherapy for a previous H&N cancer.

METHODS

Data gathering and database
Data were obtained from the Netherlands Cancer Registry (NCR). Our study retrospectively reviewed patients with cancer in the upper third of the esophagus, 18-24 cm from the incisor teeth (C15.3) and the cervical esophagus (C15.0, CEC), which is up to 18 cm distant from the incisor teeth were included, diagnosed in the period 1989-2014. Patients with metastatic disease at primary diagnosis were excluded, since they have a lower Overall Survival (OS) and would therefore bias the results. The cohort consisted of 2184 patients, of which 202 were lost to follow-up, meaning they were alive at the end of the study, and 1992 reached the endpoint, namely death. Follow-up was complete until February 1st 2016 as this was the last moment of registration.

The first steps of the database were to set up some new variables, which were not given in the original database For example, the treatment variables which were each a dichotomous variable had to be put into one categorical/nominal variable. Treatment given within a period of 9 month after diagnosis was included in the registry. As the TNM staging has changed esophageal in 2010 in a quiet extensive way, the TNM stages of the patients were recoded to the TNM6 classification by an experienced clinical statistician into a comparable stage (27).

Statistical analyses

Type of previous tumor was analyzed for the whole population using the restructured database. Differences between expected and observed frequencies of previous tumors types between men and women and between AC and SCC were determined by a chi-square test, a z-test with Bonferroni correction was done for comparison of the properties. Time between diagnosis of previous tumor and diagnosis of PEC was compared between gender. Similarly, location of PEC (C15.0 or C15.3) was analyzed for association with previous tumor site.

Five-year OS was computed using Kaplan-Meier survival curves and comparison between groups was executed with the log-rank test. Death was the event of failure and the endpoint of the study if patients were not lost to follow-up. The follow-up time was defined as the time between the diagnosis of PEC and the censoring date, which is death or the last moment of follow-up. OS was univariately compared between patients with and those without previous tumors, between the amount of previous tumors, between the type of most recent previous tumor and between groups of time interval between PEC diagnosis and previous tumor. Multivariate analysis was executed using Cox proportional hazard model. Confounder variables were determined by comparing 5-year OS of the general population and evaluating unequal distribution of properties among patients with and without previous tumors. Covariates which were taken into the Cox proportional hazard model and their corresponding categories were morphology, clinical T stage and incidence year. Effect modification of gender and morphology was analyzed by stratifying the regression analysis by the latter variables. The obtained p-values were two-sided and a p-value below 0.05 was taken as significant.

RESULTS

General descriptive statistics of the study population and classification by previous tumor presence

In the used dataset, there were 2194 patients with PEC, of which 522 patients had cancer in the cervical region and 1672 patients had cancer in the upper third of the esophagus. The majority was male (56%) and the median age of total population was 68 years. All in all, there were 400 (18%) patients who had any previous tumor. Of these, 329 (82% of previous tumor group) patients had one previous tumor, 52 (15%) had two previous tumors, 20 had three previous tumors (5%) and three had four previous tumors (0.75%).

When comparing characteristics of patient with and without a previous tumor, there was no difference between those two groups regarding the mean of age or the distribution within age groups. There was a significant difference in groups regarding diagnosis year, as in the first two time intervals less previous tumors were diagnosed and the mean follow-up. The follow-up time was significantly lower in the previous malignancy group (1.2 years vs. 1.6 years; $p<0.05$). Patients with previous malignancies have a higher proportion of SCC in comparison to patients without a previous malignancy. Regarding TNM tumor status, there was no association observed in N and M classification, although T classification shows a significant association, which expresses in a trend towards a higher percentage of T4 status in patients without previous tumors.

There were 493 previous tumors observed in 400 patients, 280 tumors in 228 men and 213 tumors in 172 women. 58% of the tumors presented in men and 42% of tumors presented in women.

More than half of the tumors in men were H&N tumors, followed by urogenital tumors with 16% and lung cancers with 10%. GI tumors and tumors of the skin represented 8% of previous tumors, while tumors of the lymphatic system and other tumors only had a marginal proportion (2% respectively 1%). In women, H&N cancer had a lower proportion in comparison to men with 37% ($p<0.001$). Breast cancer made up exactly one quarter of previous tumors in women, while lung cancer was only present in 5% of patients, which was a significant lower portion than in men ($p=0.039$). Urogenital cancer was half as prevalent in women than in men, while a prevalence of 6% of cancers of the lymphatic system was signifianctly higher than in men ($p=0.041$).

Interval between previous tumor and the occurence of PEC

Another parameter analyzed was the time between the diagnosis of the previous tumor and the diagnosis of PEC in order to gain information about possible underlying risk factors. In men, H&N and GI cancers had the highest percentage of synchronous tumors. Skin, urogenital and lymphatic system cancers had the highest proportion of tumors being diagnosed in the interval "1 to 5 years" prior to PEC occurrence. In women, the cancer types with the highest synchronous occurrence were H&N, GI and lymphatic system cancers. Lung, H&N, skin and urogenital cancers had a comparable number of tumors within 1 to 5 years before PEC. The highest proportion of malignancies in the "6 to 10 years" interval was those of the lymphatic system and the lowest one was in the urogenital system.

Previous tumors stratified by primary tumor location

In order to investigate on possible association between the tumor location of PEC, prevalence data on previous tumors were compared between C15.0 location and C15.3 location. CEC had a significantly higher percentage of H&N cancer in comparison to tumors located in the upper thoracic esophagus ($p<0.05$). Tumors in the latter position had a slight trend of increased prevalence of GI, lung, skin, breast and urogenital cancer, but this was not significant.

Survival Analysis with Kaplan-Meier and Cox regression

The survival was lower in patients with a previous malignancy, although this was not significant ($p=0.07$) with a 1-year survival of 38% in patients with a previous tumor and 42% in patients without a previous tumor (see Figure 1).

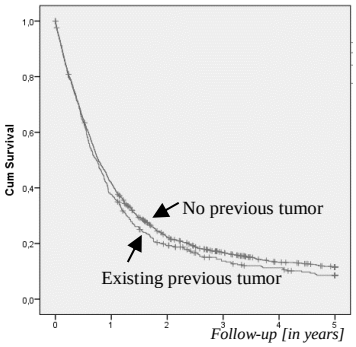

Figure 1. Survival of patients with previous tumor vs. patients without previous tumor

Five-year survival was 9% and 12% ($p=0.069$). There is a significant difference between synchronous previous tumors and tumors which are diagnosed more than 10 years before PEC ($p=0.02$), with 1-year survival rates of 30% vs. 43% and 5-year survival rates of 2% vs. 14%. Addtionally, there was a decreased survival when comparing patients without a previous tumor

and patients with a synchronous second primary cancer (p=0.031).

As the former patient group has a 1-year survival rate of 30% and the latter group a 1 year survival rate of 43% in accordance with the population without a previous tumor. Compared with patients without a previous malignancy, survival in patients with synchronous tumor was also decreased. A trend could be seen in the survival of patients depending on the amount of previous tumors, but this did not reach significant level). Only borderline significance was observated in the 5-year survival rate of patients with no previous tumor and two previous tumors (8% vs. 0%, p=0.037).Patients with more previous tumors had a lower OS than those who had less or no previous tumor.Survival was highest for patients who had previous tumor of the skin with 5-year survival rates of 20% and a median survival of 38 months. This reached significant level when compared to H&N cancer (p=0.035), GI cancer (p=0.03), lung cancer (p=0.004) and urogenital cancer (p=0.036). The lowest median survival was observed in cancers of the lymphatic system (16 month) lung (16.5 months) and GI cancer (17.8 month).

Multivariate analysis using Cox proportional hazard model

In univariate analysis, there was no significant influence of previous tumors on survival observed. Nevertheless, in multivariate analysis, there was a significant difference in the hazard ratios (HR: 1.237, CI: 1.101-1.390). When Cox regression was stratified by gender, previous tumors had an influence in survival in men and women, while this effect was stronger in women, which makes female gender an effect modificator for the effect previous tumors have on survival in patients with PEC. Cox regression was also stratified by morphology, which showed that previous tumors only had an influence on survival in patients with SCC. This could be seen in the univariate analysis, and with a higher significance in the multivariate analysis.

DISCUSSION

This research includes the largest retrospectively cohort of patients with PEC, with extensive information on previous tumors. We confirm the high prevalence of H&N cancers in the PEC population, which constitutes half of previous tumors. Men have a higher percentage of H&N cancers and lung cancer compared to women. This might be caused by a higher percentage of alcohol and tobacco use in the male population (5). In both male and female, T stage of PEC was lower in patients who had previous tumors, implicating a diagnosis due to screening or a faster intervention in case of complaints. This was in concordance with a study by Natsugoe et al. who found an earlier T stage in patients with a previous tumor (6).

Kaplan-Meier-Curves did show that there is a trend towards decreased survival in patients with previous tumors, although this was not statistically significant. Additional multivariate analysis by means of a Cox proportional hazard regression showed that survival was statistically significant decreased in both men and women with previous tumors, with a stronger effect in women. This could be due to the fact that men had a worse basic survival in comparison to women and than the effect of a previous tumor does not score as high as in women.

Léon et al. found that the survival of patients with H&N cancer decreases with number of subsequent tumors (7). Although in our dataset we looked retrospectively on previous tumors, while this study investigated on development of subsequent cancers, the consensus is comparable and the existence of multiple primary cancers decreases OS tremendously. In our analysis there also was a trend towards a proportional decrease of survival depending on the amount of previous tumors. A study on previous tumors in esophageal cancer done by Lo et al. has shown that H&N cancers appear in 7 % of ESCC and more often in men and the most prevalent tumor within the H&N cancer group was hypopharyngeal cancer (8). In our study, 8% of the total population of PEC did have a second primary H&N cancer. We also showed that patients with CEC did have a more pronounced prevalence of H&N cancer, which supports the theory of field cancerization as the cervical esophagus is closer to the H&N area. Also in line with our study was a significantly lower OS in patients with previous H&N cancer than in patients without a previous cancer. It is important to note that the high prevalence of some tumors might not be caused mainly due to the risk factors, but because an inherent increased lifetime risk of some tumors. This especially holds true for prostate cancer and breast cancer, which have one of the highest prevalences amongst cancers in the general population for men and women respectively (9). It is crucial to be aware of this fact in order to avoid over-interpretation of our data. Within our study we intended to compare our prevalences of the different tumors with data of the general healthy Dutch population, but this turned out to be more complicated than previously expected and was therefore kept for future studies.

A strength of the present study is that is has extensive data on a specific and rare type of esophageal cancer with comprehensive information of the associated previous tumors during a more than 20-year lasting follow-up period. These previous tumors might have comparable risk factors as those of PEC and can therefore give insights into the concept of field cancerization in PEC and H&N cancer. The research strategy is unique within the field of PEC as to our knowledge no study exists which considers patients' past tumor history.

Associated with this, we acknowledge an important limitation in the retrospective nature of our study, considering we can not provide an overview of the subsequent tumors associated with PEC. It might be of interest to know more about other tumors patterns after the diagnosis of PEC. Literature shows that patients with a tumor in the aerodigestive tract have a high risk of other primary tumors in that area, especially when exposure to risk factors continues after diagnosis of the index tumor (10, 11).

Our study has shown that especially previous H&N tumors can have a large impact in cancers of the proximal esophagus as they decrease survival in both men and women and therefore worsen clinical outcome in patients diagnosed within the curative setting, i.e. non-metastasized disease. These results can affect clinicians to take patients' previous tumor history into account during treatment decision-making. This especially holds true for tumors which occurred within the 5-year interval of the diagnosis of PEC. In order to be able to distinguish second primary tumor from metastasis or recurrent there needs to be consensus on the used definitions. In our study, tumors were classified as being synchronous when they were in the same calendrary year. Of course this gives the possibility of a tumors being nearly two years apart and still classified as a synchronous tumor and on the other hand, tumors which occurred in the end and in the beginning of the subsequent year, are also misclassified as they are only seperated by a few month.

Further studies are needed to investigate further on the pattern of occurrence of previous tumors and together with data of the histopathology of the previous tumor and exposed risk factors, prediction (models) of PEC should be set up. The comparative study by de Vos-Geelen et al. about different

regimes of definitive chemoradiation is ongoing, but study results were not sufficiently available until the end of this research period. This study includes parameters like comorbidities, smoking and alcohol consumption, previous and subsequent malignancies and therefore could serve to gain further knowledge of the association between the previous mentioned factors and associated tumors of PEC which could then be used to improve prevention of PEC. Likewise, some other studies come to the conclusion that stringent surveillance for malignancies is important in patients with H&N cancer, particularly in those with hypopharyngeal cancer, as patients with this type of cancer are most likely to develop ESCC (12). For successful implication into the clinic it is of utmost importance that all diagnostic modalities are used for tumor staging and that an appropriate (molecular) distinction is being made between a previous primary tumor in order to treat the patient according to the correct setting (13). A smooth cooperation between the general physician and the different specialists in the clinic is crucial for appropriate patient information transfer and ro avoid information gaps regarding previous tumor history. This would be an important step towards the prevention of PEC and improvement of survival and quality of life in cancer patients.

CONCLUSION

In this study we showed that patients with PEC have a high prevalence of previous tumors with an influence on OS. In addition to continued exposure to similar risk factors, the term field cancerization is a possible explanation for the high prevalence of second tumors in this population. More research is needed to explore the effectiveness of strict prevention and surveillance programs, which could contribute to a decreased rate of PEC and detect this cancer in an earlier stage.

ROLE OF THE STUDENT (MANDATORY)

My role in this project was to analyze data of the IKNL database, which means that I first recoded certain variables, grouped values and executed frequency analysis, Kaplan Meier Survival Curves and Cox regression.

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