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# Clinical characteristics and survival of patients with multiple metachronous esophageal tumor

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ABSTRACT

*Background:* The aim of this study is to determine the clinical characteristics and predictors of survival for patients with multiple metachronous esophageal tumors (MMET) and to compare the survival with patients that have single esophageal tumor (SET).

*Method:* We identified all cases of primary esophageal cancer from the Surveillance, Epidemiology and End Results program database from 2000 to 2013. The primary outcome was the development of a second esophageal cancer six months after the diagnosis of the first tumor. A secondary outcome was disease-specific death from esophageal cancer. Chi-square test was used to compare the tumor and demographic characteristics of patients with SET versus the first and second tumor characteristics of patients with MMET. Logistic regression was used to obtain the odds ratios between patients with secondary tumors and those with primary tumors. Accelerated life model was performed for patients with MMET to determine the predictors of survival.

*Results:* Patients with MMET were more likely to have localized stage disease compared to those with SET ($P < 0.0001$). Distant stage disease for both first tumor ($\beta = -0.402$, $P = 0.003$) and second tumor ($\beta = -0.301$, $P = 0.033$) were predictors of increased mortality. The interval between the first and second tumor affected survival. Intervals of 2–5 years and > 5 years were associated with a reduced hazard with a $\beta = 0.53$ and 1.13, $P < 0.0001$, respectively.

*Conclusion:* Early development of a second tumor in MMET is associated with poorer survival. Patients with MMET may benefit from regular follow-up and intervention to prevent the development of a second tumor.

## 1. Introduction

Warren and Gates defined multiple primary tumors as the occurrence of two histopathological tumors separated by a mucous membrane with each tumor not resulting from extension or metastasis of the other tumor [1,2]. The occurrence of multiple primary malignancies has been increasing since they were first discovered by Billroth in 1860 [[3]–[5]]. The increase in the prevalence of these malignancies is mainly due to improve diagnostic capability and longer patient survival. Multiple primary malignancies lead to further complication of patient management, increase morbidity and mortality and challenges in the management of patients with cancer.

The most common theory used to explain the occurrence of multiple tumors is field cancerization. [6–8] Tumors don't arise from a single cellular event or damage but develop from a pathological process involving many cells from a wide area or field defect due to exposure from a carcinogen [[6]–[8]]. Multiple cancers could thus arise from this area of field defect either at the same time (synchronously) or at different time points (metachronously) [6,7].

Esophageal cancer is the 18th most common cancer in the United States, but it is among the top 10 causes of cancer-related death in the United States [9]. Its five-year survival is estimated to be at around 18% [9]. Studies have shown that having a second tumor in the esophagus is associated with increased mortality [10,11]. Li and Lin [12] have shown that patients with synchronous multiple esophageal cancer have a five-year survival rate of 17.3% and they also found that having chemotherapy and localized stage disease were associated with better survival. Other studies on multiple esophageal cancers looked at the histopathological features of the tumors [13,14]. However, these studies did not explore the survival of patients with metachronous esophageal cancer and how it may differ from patients with single tumors.

We hypothesize that the clinical characteristics of patients with single esophageal tumors should be different from MMET and patients with the former should have a better survival compared to the latter.

*Abbreviations:* MMET, multiple metachronous esophageal tumors; SET, single esophageal tumor; SEER, surveillance epidemiology and end-result survey program

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We will study this hypothesis through the following: (1) identifying the risk factors for MMET; (2) comparing the survival of MMET versus SET; and (3), determining the factors that predict survival in metachronous esophageal cancer.

## 2. Methods

Data was obtained from the 18 cancer registries in the Surveillance, Epidemiology, and End Results (SEER) program from 2000 to 2013 [9]. The SEER data contains a population-based sample of cancer incidence and mortality, and represents about 30% of the US population. The data also contains demographic variables, treatment history and tumor characteristics that are important for prognostication [9]. The SEER data has rules and guidelines regarding coding of multiple primary cancer and is, therefore, appropriate for this analysis [15].

We identified all cases of primary esophageal cancer in the data set, and these cases were followed up for the development of a metachronous second esophageal cancer. This was defined as a second esophageal tumor occurring after six months of diagnosing the first tumor [16,17]. A secondary outcome was disease-specific death from esophageal cancer. Cases with unknown age and cases diagnosed at autopsy were excluded.

Several demographic and clinical variables were used in the analysis. The variables used include age at diagnosis, year of diagnosis, race, sex, treatment, stage, site, histology and grade. Age at diagnosis was categorized into quartiles: 20–57, 58–65, 66–73 and older than 73. Because of small sample sizes of some of the categories in our variables for patients with MMET, the following categories were modified: Blacks and Asian Americans were grouped together as others; well differentiated and moderately differentiated were grouped as group I/II while poorly differentiated and undifferentiated were grouped together as group III/IV. Treatment information from SEER data is restricted to only radiation therapy and surgery. Patients who received either one of those or both were considered to have received some form of treatment. Staging of esophageal cancer is based on the SEER historic stage [9] and comprises of localized, regional, distant and unstaged. The International Classification of Disease, ICD-O3 [9] morphology was used to identify squamous cell carcinoma (8050–8084) and adenocarcinoma (8140–8175).

Bivariate analysis based on Chi-square test was used to compare the tumor and demographic characteristics of patients with SET versus the first and second tumor characteristics of patients with MMET. Logistic regression was used to determine odds ratios for different risk factors among patients with secondary tumors versus those with primary tumors. Likelihood ratio test was used to select variables in the model.

Both SET and MMET cases were followed up during the study period to determine their subsequent survival. We measured Survival time from date of diagnosis to date last known to be alive, date of death or end of study period (31 December 2013).Those who were alive at the cut-off date or last follow-up date were censored. We compared Kaplan-Meier plots for both patients with SET and patients with MMET. This was further stratified by stage of diagnosis for both MMET and SET as well as latency between first and second tumor for MMET. Accelerated life model based on a lognormal distribution was performed for patients with MMET to determine factors that predict their survival. Plots of residuals and log likelihood ratio test were used to select variables for inclusion in the model. The final survival model included latency, year of diagnosis, grade, stage of the first tumor, stage of second tumor and histology. Analyses were done using SAS 9.3 (SAS Institute Inc., Cary, NC) and R Studio. We reported two-sided P-values.

## 3. Results

Table 1 is a summary of the descriptive characteristics comparing patients with SET and MMET. A total of 23,793 patients had a single esophageal tumor while 116 had MMET. Patients with SET and MMET were more likely to be White and males. There was no significant difference in tumor site for SET compared to the first tumor in MMET ($P = 0.115$), but not the second tumor ($P < 0.0001$). Most of the patients (98%) who developed a second tumor did not receive surgery or radiotherapy. Patients with MMET were more likely to have localized stage disease compared to those with SET ($P < 0.0001$). The logistic regression (Table 2) also confirms this where patients with MMET had lower odds of having regional and distant stage disease (OR = 0.64, 95%CI: 0.41–0.98 and OR = 0.27, 95%: 0.15–0.48, respectively).

Table 3 is a summary of the accelerated life model for survival in patients with metachronous esophageal tumors. Distant stage diseases for both first tumor ($\beta = -0.402$, $P = 0.003$) and second tumor ($\beta = -0.301$, $P = 0.033$) were predictors of increased mortality. The interval between the first and second tumor affected survival. Intervals of 2–5 years and > 5 years were associated with a reduced hazard with a $\beta = 0.53$ and 1.13, $P < 0.0001$, respectively. Poorly differentiated tumors did not increase mortality ($P = 0.235$).

Kaplan-Meier plots indicate an overall better initial survival for patients with MMET compared to those with SET (Fig. 1). The median survival for MMET was 64 months and 19 months for SET (Supplementary Table). Kaplan–Meier plots also indicate that developing a second tumor within two years was associated with higher mortality compared to those who develop tumors within 2–5 years and more than five years (Fig. 2). Because stage appeared to be an important predictor of survival and we also found that patients with MMET are more likely to have localized stage disease, we performed KM plots comparing SET and MMET by stage specifically for localized and distant stage disease. These plots also show that regardless of stage, patients with MMET have better survival compared to patients with SET (Fig. 3). Median survival times for localized and distant stages were higher for MMET (65 months and 23 months, respectively) than for SET (56 months and 12 months, respectively) (Supplementary Table).

## Discussion

Our main study objective was to determine the clinical risk factors associated with MMET and to compare the survival of patients with MMET versus SET. We found that patients with MMET were more likely to have early stage disease compared to patients with SET. This is similar to the findings by Li and Lin et al. where they found that 85% of their patients with multiple esophageal tumors had no metastasis [12]. Pesko et al. studied the clinical and pathological features in 54 patients with esophageal cancer, seventeen of which had metachronous esophageal cancer [14]. They found a greater depth of invasion of the first tumor compared to the second tumor ($P < 0.01$) implying that the first tumor needs to be present for a considerable period before the second tumor develops [14]. This was similar to another study which found the second esophageal tumor to be considerably deeper compared to the first esophageal tumor [13]. Patients with MMET are therefore more likely to have early-stage disease and require a certain period to develop the second tumor. Because of the poor survival of patients with advanced stage esophageal disease compared to localized disease, they do not live long enough to develop a second tumor. This may explain the better initial survival we observed in patients MMET compared to those with SET.

The main predictors of survival in those with MMET were distant stage disease of the first and second tumor and early development of the second tumor. Distant stage disease has been recognized as a poor prognostic factor in patients with multiple tumors including esophageal cancer [12,18]. Interestingly, we found that those with MMET who developed their second tumor within a shorter interval had a poorer prognosis. All those who developed a second tumor within two years died before the end of the study period, while 14% and 20% survived up to the end of the study period in those who developed their second tumor between 2–5 years and > 5 years, respectively. We, therefore, concluded that, even though patients with MMET are more likely to