Original Article

Clinical-Pathological Characteristics and Prognosis of a Cohort of Oesophageal Cancer Patients: a Competing Risks Survival Analysis

Elena Rodríguez-Camacho, Salvador Pita-Fernández, Sonia Pértega-Díaz, Beatriz López-Calviño, and Teresa Seoane-Pillado

Clinical Epidemiology and Biostatistics Research Group, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), SERGAS, Universidade da Coruña, Coruña, Spain

Received June 22, 2014; accepted October 18, 2014; released online January 19, 2015

Copyright © 2015 Elena Rodríguez-Camacho et al. This is an open access article distributed under the terms of Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

Background: To determine the clinical course, follow-up strategies, and survival of oesophageal cancer patients using a competing risks survival analysis.

Methods: We conducted a retrospective and prospective follow-up study. The study included 180 patients with a pathological diagnosis of oesophageal cancer in A Coruña, Spain, between 2003 and 2008. The Kaplan-Meier methodology and competing risks survival analysis were used to calculate the specific survival rate. The study was approved by the Ethics Review Board (code 2011/372, CEIC Galicia).

Results: The specific survival rate at the first, third, and fifth years was 40.2%, 18.1%, and 12.4%, respectively. Using the Kaplan-Meier methodology, the survival rate was slightly higher after the third year of follow-up. In the multivariate analysis, poor prognosis factors were female sex (hazard ratio [HR] 1.94; 95% confidence interval [CI], 1.24–3.03), Charlson’s comorbidity index (HR 1.17; 95% CI, 1.02–1.33), and stage IV tumours (HR 1.70; 95% CI, 1.11–2.59). The probability of dying decreased with surgical and oncological treatment (chemotherapy and/or radiotherapy) (HR 0.23; 95% CI, 0.12–0.45). The number of hospital consultations per year during the follow-up period, from diagnosis to the appearance of a new event (local recurrences, newly appeared metastasis, and newly appeared neoplasias) did not affect the probability of survival (HR 1.03; 95% CI, 0.92–1.15).

Conclusions: The Kaplan-Meier methodology overestimates the survival rate in comparison to competing risks analysis. The variables associated with a poor prognosis are female sex, Charlson’s comorbidity score and extensive tumour invasion. Type of follow-up strategy employed after diagnosis does not affect the prognosis of the disease.

Key words: oesophageal neoplasms; therapeutics; survival; follow-up studies

INTRODUCTION

Oesophageal cancer is the eighth-most common cancer worldwide. In the 27-member European Union, a total of 33 013 new cases were estimated in 2008 (age-standardised rate for world population [ASR{W}]: 3.5 per 100 000). In relation to the rest of Europe, Spain is at a midway point in terms of occurrence (ASR[W]: 2.8 per 100 000). Within Spain, this cancer occurs at a higher rate in the country’s northern regions than in southern ones.

At the worldwide level, oesophageal cancer is the sixth-most frequent cause of death by cancer. In 2008, the global age-standardised rate of cancer-related mortality was 2.9 per 100 000 inhabitants in the European Union and 2.3 per 100 000 in Spain. The mortality rate, like the occurrence rate, is higher in Spain’s northern regions.

According to the European Cancer Registry EUROCARE-4 study, the average European survival rate is close to 35% at one year and close to 10% at 5 years, and survival is strongly associated with the clinical stage of the tumour and the treatment the patient receives. There is little consensus when it comes to defining the follow-up protocols for these patients. Furthermore, to the best of our knowledge, there are no observational or experimental studies that have investigated the role of the different follow-up strategies on these patients’ prognosis.
With regard to analysing the survival rate, competing risk models are the most suitable for analysing the behaviour of subjects who may die for different reasons. However, when applied in the presence of competitive risks, the usual techniques for analysing the time until the event, such as the Kaplan-Meier methodology, produce biased results.\textsuperscript{9,10} By using specific techniques, it is possible to reduce bias so that results can be correctly interpreted.

Therefore, the geographic variability in the occurrence and mortality rates, the existence of different risk factors associated with the low survival rate for these kinds of tumours, and the lack of consensus with regard to optimum follow-up strategies justify the undertaking of this study. The aim of the study was to identify the epidemiology of oesophageal cancer in the area of A Coruña, Spain, the supportive process applied to these patients, and their prognosis, using the competing risks methodology.

**METHODS**

A total of 234 patients were included in the study, with anatomical-pathological confirmation of cancer of the oesophagus diagnosed at the University Hospital Complex in A Coruña, Spain between the 1st of January, 2003, and the 31st of December, 2008. A retrospective review of the patients’ clinical records was carried out together with a prospective follow-up until the 31st of January, 2012, in order to guarantee a minimum follow-up period of 3 years. The study excluded prevalent or recurring cases, subjects with multiple or metastatic cancers, or those that had been treated and/or diagnosed at other hospitals. After exclusions, the final study sample comprised 180 patients.

**Measurements**

We collected information on the socio-demographic variables of the patient, their personal backgrounds, comorbidity variables using Charlson’s comorbidity index, the symptoms present at diagnosis, location of the tumour, histopathologic cell type, and tumour stage (TNM, seventh edition).\textsuperscript{11,12} As data on risk factors and symptoms were collected retrospectively from electronic hospital clinical records, we registered data that were indicated in the clinical records but could not quantify the frequency and amount of cigarette or alcohol consumption, nor the number of kilograms lost during the previous months before the diagnosis.

We also collected data on the treatment received (surgery, chemotherapy, and radiotherapy), as well as the visits and tests carried out during the follow-up period: consultations and hospital stays, endoscopies, computer-aided tomography scans, and thorax X-rays. Also, the presence of follow-up events, including newly appeared local recurrences, metastasis, and neoplasias, was studied. For all dead patients, cause of death was obtained from the Galician Mortality Registry (General Directory of Public Health, Xunta de Galicia, Spain), according to the 21 diagnostic categories of the 10th revision of the International Classification of Diseases.

**Sample size justification**

The study included a total of 180 patients. This sample size makes it possible to detect as significant a hazard ratio of 1.6 or more, with a prevalence of exposure of 50% and a censored data percentage of 20% (security: 95%; statistical power: 80%).

**Statistical analysis**

A descriptive study was made of the variables that were obtained. The specific survival rate was calculated using the Kaplan-Meier methodology and competing risks survival analysis. The accumulated occurrence of dying as a result of oesophageal cancer during the follow-up period was estimated, considering death as a result of other causes as a competitive event, using the method proposed by Kalbfleisch and Prentice.\textsuperscript{13} The accumulated occurrence of death due to oesophageal cancer according to different characteristics was compared using the test proposed by Gray.\textsuperscript{14} Finally, in order to identify which characteristics were associated with the risk of dying as a result of oesophageal cancer, a multivariate analysis was carried out using the model proposed by Fine and Gray.\textsuperscript{15} All of the tests were carried out bilaterally, considering values of $P < 0.05$ as significant. The analyses were carried out using the programmes Epidat 3.1 (Xunta de Galicia, Santiago de Compostela, Spain), SPSS 19.0 (IBM Company, Chicago, IL, USA), and R 2.15.1 (Free Software Foundation, Boston, MA, USA).

**Ethics**

The study was carried out according to the principles laid down in the Declaration of Helsinki and ensuring compliance with Spanish Decree 29/2009, which regulates the use of and access to electronic medical records. Confidentiality was maintained in accordance with the current Spanish Data Protection Law (15/1999). The study received written approval from the regional Ethics Committee for Clinical Research (code 2011/372 CEIC Galicia).

**RESULTS**

**Characteristics of the patients studied**

Table 1 shows the baseline characteristics, comorbidities, and cause of death of the patients. The median age was 64.5 years, 87.8% of the sample subjects were male, 58.6% had a body mass index (BMI) within normal range, and 11.4% were obese. The most frequent symptom reported was dysphagia (82.0%), followed by weight loss (49.4%). Regarding tumour stage, 46.8% of the tumours were moderately differentiated, 38.0% were poorly differentiated, and 28.9% had metastasis at the time of diagnosis (Table 2).
Treatments involved chemotherapy and/or radiotherapy exclusively in 36.1%, surgery as the sole treatment in 23.3%, and a combination of both in 19.4% (Table 2). In the case of patients who only received surgery, resection was carried out for curative purposes in 74%. Both chemotherapy and radiotherapy were mainly applied for palliative purposes.

The specific survival rate at 1, 3, and 5 years after diagnosis obtained with the Kaplan-Meier methodology was 39.9%, 19%, and 15%, respectively, while respective survival rates according to competing risks survival analysis were 40.2%, 18.1%, and 12.4% (Table 3).

At 1 year from diagnosis, the probability of dying as a result of the cancer was 59.2%, with the probability of dying from other causes being 0.6% (Figure). At 5 years from
diagnosis, the probability of dying as a result of the cancer rose to 83.4% and the probability of dying from other causes was 4.2%; therefore, the probability of survival was reduced to 12.4%.

The variables in the univariate analysis that were significantly associated with the probability of dying during the follow-up period were: gender, Charlson’s comorbidity index, presence of weight loss, histopathological cell type, tumour stage, and type of treatment (Table 3). The specific probability of dying was increased among females (hazard ratio [HR] 1.63; 95% CI, 1.00–2.64), those with a higher score on age-adjusted Charlson’s comorbidity index (HR 1.14; 95% CI, 1.05–1.23), and among those with weight loss on diagnosis (HR 1.68; 95% CI, 1.20–2.34). The histopathologic cell type with the highest mortality rate was adenocarcinoma (HR 1.68; 95% CI, 1.08–2.62). In turn, those with stage IV tumours had a higher mortality rate than those in earlier stages (0-III) (HR 2.38; 95% CI, 1.63–3.46).

The patients who had received some kind of treatment had a lower probability of dying. Those who had received a combination of surgical and oncological treatment (chemotherapy and/or radiotherapy) had the lowest probability of dying (HR 0.17; 95% CI, 0.10–0.27), followed by those who had only received surgical treatment (HR 0.22; 95% CI, 0.12–0.38).

No association was found between the probability of dying during the follow-up period and the following variables: year of diagnosis, age, BMI, personal background (smoking, regular alcohol consumption, gastro-oesophageal reflux, achalasia, and a family history of cancer), presence of dysphagia on diagnosis, or tumour location.

**Table 2. Tumour characteristics, TNM classification, and treatment options of the patients studied**

| Tumour location          | n  | %   | 95% CI            |
|--------------------------|----|-----|-------------------|
| Cervical                 | 15 | 8.3 | 4.0–12.7          |
| Upper thoracic           | 37 | 20.6| 14.4–26.7         |
| Middle thoracic          | 58 | 32.2| 25.1–39.3         |
| Lower thoracic           | 54 | 30.0| 23.0–37.0         |
| Distal oesophagus        | 16 | 8.9 | 4.5–13.3          |

| Histopathologic cell type| n  | %   | 95% CI            |
|--------------------------|----|-----|-------------------|
| Squamous-cell carcinoma  | 147| 81.7| 75.7–87.6         |
| Adenocarcinoma           | 32 | 17.8| 11.9–23.6         |
| Malignant tumor of unknown histology | 1 | 0.6 | 0.0–3.1 |

| TNM classification        | Stages 0-III | 128 | 71.1 | 64.2–78.0 |
|---------------------------|--------------|-----|------|-----------|
| Stage IV                  | 52           | 28.9| 22.0–35.8 |

| Treatment            | No treatment | 38  | 21.1 | 14.9–27.4 |
|----------------------|--------------|-----|------|-----------|
| Surgery              | 42           | 23.3| 16.9–29.8 |
| Chemotherapy and/or Radiotherapy | 65 | 36.1| 28.8–43.4 |
| Surgery and Chemotherapy and/or Radiotherapy | 35 | 19.4| 13.4–25.5 |

CI, confidence interval.

**Table 3. Univariate analysis of variables associated or not with cancer-related mortality during the follow-up and survival rate with Kaplan-Meier and competing risks analysis methods**

| Oesophageal cancer-related mortality | No | Yes | P  | HR  | 95% CI |
|-------------------------------------|----|-----|----|-----|--------|
|                                     | n  | Mean| SD | Median | n  | Mean| SD | Median |  |
| Age (years)                         | 28 | 63.7| 8.8 | 65.0  | 150| 64.3| 11.6| 64.0  |
| Charlson’s comorbidity index age adjusted | 28 | 2.7 | 1.3 | 3.0   | 150| 3.3 | 1.9 | 3.0   |

| Probability of mortality (%) (Oesophageal cancer-related) | No | Yes | P  | HR  | 95% CI |
|-----------------------------------------------------------|----|-----|----|-----|--------|
| 6 months                                                  | 28 | 33.1| 56.9| 78.2 | 81.7  |
| 1 year                                                    | 150| 47.6| 76.2| 90.5 | 95.2  |
| 3 years                                                  | 150| 24.8| 46.4| 72.7 | 80.5  |
| 5 years                                                  | 150| 44.8| 72.4| 87.4 | 87.4  |
| Gender                                                    |    |     |     |      |       |
| Male                                                      | 33.1| 56.9| 78.2| 81.7 | —     |
| Female                                                   | 47.6| 76.2| 90.5| 95.2 | 0.050 | 1.63  |
| Weight loss                                               |    |     |     |      |       |
| No                                                        | 24.8| 46.4| 72.7| 80.5 | —     |
| Yes                                                       | 44.8| 72.4| 87.4| 87.4 | 0.002 | 1.68  |
| Histopathologic cell type                                 |    |     |     |      |       |
| Squamous-cell carcinoma                                   | 31.0| 55.2| 77.2| 80.9 | —     |
| Adenocarcinoma                                           | 53.3| 76.7| 90.0| 93.3 | 0.021 | 1.68  |
| TNM classification                                        |    |     |     |      |       |
| Stages 0-III                                             | 27.0| 49.5| 73.5| 78.1 | —     |
| Stage IV                                                 | 53.9| 82.7| 94.2| 96.2 | <0.001| 2.38  |
| Treatment                                                |    |     |     |      |       |
| No treatment                                             | 73.0| 97.3| —   | —    | —     |
| Surgery                                                  | 31.7| 59.6| 69.7| 73.9 | <0.001| 0.22  |
| Chemotherapy and/or Radiotherapy                         | 27.7| 53.8| 83.1| 84.6 | <0.001| 0.26  |
| Surgery and Chemotherapy and/or Radiotherapy             | 11.4| 28.6| 62.9| 74.8 | <0.001| 0.17  |

| Survival Rate (Oesophageal cancer-related) | 1 year | 3 years | 5 years |
|-------------------------------------------|--------|---------|---------|
| Kaplan-Meier survival rate                | 39.9%  | 19.0%   | 15.0%   |
| Competing risks survival rate             | 40.2%  | 18.1%   | 12.4%   |

CI, confidence interval; HR, hazard ratio; SD, standard deviation.

J Epidemiol 2015;25(3):231-238
According to the final adjustment by multivariate competing risks analysis, we found that the variables with an independent effect to predict mortality are gender, Charlson’s comorbidity index, and tumour stage (Table 4). In order to adjust for age as a clinically relevant and confounding variable and avoid over-adjustment, we included in the model the crude Charlson’s comorbidity index. The specific probability of dying from oesophageal cancer was increased among females (HR 1.94; 95% CI, 1.24–3.03), those with a higher score on Charlson’s comorbidity index (HR 1.17; 95% CI, 1.02–1.33), and in those with stage IV tumours at the time of diagnosis (HR 1.70; 95% CI, 1.11–2.59). Having received some type of treatment improved the prognosis, with a greater impact in cases that received a combination of surgical and oncological treatment (HR 0.23; 95% CI, 0.12–0.45). Furthermore, no significant effect was found when the interaction between TNM classification and type of treatment was added to the multivariate model ($P = 0.600$).

**Table 4. Multivariate analysis of oesophageal cancer-related mortality adjusting for different variables**

| Variables                                  | B     | SE    | $P$   | HR    | 95% CI       |
|--------------------------------------------|-------|-------|-------|-------|--------------|
| Gender (Female vs. Male)                   | 0.660 | 0.229 | **0.004** | 1.94 | (1.24–3.03)  |
| Age (years)                                | −0.006| 0.007 | 0.380 | 0.99  | (0.98–1.01)  |
| Charlson’s comorbidity index               | 0.153 | 0.066 | **0.021** | 1.17 | (1.02–1.33)  |
| Weight loss                                | 0.301 | 0.185 | 0.100 | 1.35  | (0.94–1.94)  |
| Histopathologic cell type (AC vs. SCC)     | 0.434 | 0.233 | 0.063 | 1.54  | (0.98–2.44)  |
| TNM classification (IV vs. 0-III)          | 0.529 | 0.216 | **0.014** | 1.70 | (1.11–2.59)  |
| Treatment                                  |       |       |       |       |              |
| Surgery                                    | −1.305| 0.314 | <**0.001** | 0.27 | (0.15–0.50)  |
| Chemotherapy and/or Radiotherapy           | −1.076| 0.249 | <**0.001** | 0.34 | (0.21–0.56)  |
| Surgery and Chemotherapy and/or Radiotherapy| −1.466| 0.340 | <**0.001** | 0.23 | (0.12–0.45)  |

AC, adenocarcinoma; B, regression coefficient; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SE, standard error.
Follow-up

The total length of follow-up was 3221.8 months (268.5 years), with a mean of 9.4 months per patient. The most frequently detected events during follow-up were newly appeared metastasis (19.0%)—mainly located in the lungs (48.5%)—and local tumour recurrences (16.7%) (Table 5).

In those patients who underwent curative surgery, the probability of being diagnosed with a tumour recurrence (local tumour recurrence, distant recurrence, or both) during the follow-up period was 3221.8 months (268.5 years), with a mean of 9.4 months per patient. The most frequently detected events during follow-up were newly appeared metastasis (19.0%)—mainly located in the lungs (48.5%)—and local tumour recurrences (16.7%) (Table 5).

When we take into account gender, age, Charlson’s comorbidity index, weight loss, histopathological cell type, TNM stage, treatment carried out, and number of consultations per follow-up year, in the interval between the diagnosis until an event occurs, we see that the consultations carried out during this period do not substantially alter the likelihood of survival ($P=0.640$; HR 1.03; 95% CI, 0.92–1.15).

Table 5. Appearance of new events during the follow-up

| Event                          | n   | %  |
|-------------------------------|-----|----|
| Local tumor recurrence        | 29  | 16.7|
| Newly appeared metastases     | 33  | 19.0|
| Newly appeared neoplasias     | 5   | 2.9 |

Table 6. Follow-up strategies, from diagnosis to the appearance of a new event, in patients who underwent curative intent surgery

| Strategy                               | Mean  | SD   | Median | IQR   |
|----------------------------------------|-------|------|--------|-------|
| Number of hospital consultations/patient/year | 4.1   | 4.2  | 3.1    | 0.7–5.9 |
| Number of endoscopies/patient/year     | 1.3   | 2.4  | 0.3    | 0.0–1.4 |
| Number of thorax X-rays/patient/year   | 8.8   | 26.0 | 2.3    | 0.3–8.1 |
| Number of CAT scans/patient/year       | 1.4   | 4.9  | 0.0    | 0.0–0.9 |
| Number of hospital stays/patient/year  | 1.9   | 2.4  | 1.0    | 0.0–3.0 |

CAT, computer-aided tomography; IQR, inter-quartile range; SD, standard deviation.

DISCUSSION

In Spain, the occurrence of oesophageal cancer is at a midway point with regard to the rest of Europe. It is more frequent in men and usually appears between the ages of 55 and 70 years, and the most common symptom associated with its appearance is dysphagia. The results of the present study confirm these findings and are in line with those of other previously published series, which reported 5-year survival rates of 8.8% and 12%, respectively. Series published in Europe, such as those in Sweden, England, and France found similar figures, with 5-year survival rates between 9.3%–13.1%, 3.2%–9.8%, and 9%–14%, respectively. In our study, the 5-year survival rate was 12.4%. It is important to note that we used the competing risks survival analysis method in our study, which is suitable for analysing the behaviour of a person who may die as a result of different causes. Using the Kaplan-Meier methodology, the results obtained for our sample slightly overestimated the survival rate from the third year onwards. The patients in this cohort mainly die as a result of the illness in question, and so for this reason the differences found in the survival rate between the Kaplan-Meier methodology and competing risks survival analysis are very low. Despite this, the competing risks survival analysis method is the most suitable for analysing the specific survival rate in the presence of other causes of death. This overestimation of the survival rate using the Kaplan-Meier methodology in comparison to competing risks survival analysis has previously been described in the literature.

With regard to the factors associated with survival, most studies have indicated that women have higher survival rates than men, although in some studies these differences were not significant. In a study of patients from the Donostia Hospital in the Basque Country, Spain, the mean survival rate in women was lower, as in our study, although the differences were not significant. In our study, we found that the patient’s number and severity of comorbidities, assessed using Charlson’s comorbidity index, is significantly associated with the likelihood of dying as a result of the tumour. In a recent study in the Netherlands, having comorbidities was associated with poor survival, as in our study, although no significant differences were found.

Amongst the limitations to the study, we did not study any molecular marker that could play an important role in the prognosis of oesophageal cancer and which, in combination
with other parameters such as tumour stage, would help to identify and predict the survival rate from these tumours, as well as to individually adapt the treatment to each patient, as recently described in the literature.28,29 Although our sample only consisted of 180 patients, we were able to compare the consistency of our results with larger series published internationally,5–7,20,23,24,30–32 in which the tumour stage and treatment received by the patient were the main prognostic factors for survival.

This study reveals how the different follow-up strategies used (visits and tests carried out) in patients where the intention is to apply curative treatment until a new event occurs do not alter their survival rate. This finding is in agreement with the lack of consensus at the international level8,33,34 in terms of defining the follow-up protocols for these types of tumours. Furthermore, we did not find any studies in the literature that describe the follow-up process applied to these patients and its possible effect on their survival rate. In The European Society for Medical Oncology’s guidelines for the diagnosis, treatment, and monitoring of oesophageal cancer for 2013,35 the group concluded that, with the exception of patients who could be candidates for rescue surgery after a failed endoscopic resection or definitive chemo-radiotherapy, there is no evidence that regular follow-up after the initial therapy impacts the final outcome.

In conclusion, the specific survival rate detected in our study was low and coincided with figures published at the international level. Our results confirm that studying the survival rate using the Kaplan-Meier methodology overestimates the survival rate in comparison to competing risks survival analysis. We also found that the different follow-up strategies used after diagnosing illness in patients who are surgically treated with the intention to cure do not alter the prognosis.

ACKNOWLEDGMENTS

This work was partially supported by the Post-Specialization Scholarship of the Professor Novoa Santos Foundation (A Coruña, Spain).

Conflicts of interest: None declared.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No.10 [Internet]. Lyon, France: International Agency for Research on Cancer 2010 [access:29.10.2013]. Available at: http://globocan.iarc.fr.
2. Cabanes A, Pérez-Gómez B, Aragonés N, Pollán M, López-Abente G. The situation of cancer in Spain, 1975–2006. Madrid: Instituto de Salud Carlos III; 2009 (in Spanish).
3. Aragonés N, Ramis R, Pollán M, Pérez-Gómez B, Gómez-Barroso D, Lope V, et al. Oesophageal cancer mortality in Spain: a spatial analysis. BMC Cancer. 2007;7:3.
4. Sant M, Allemani C, Santausilani M, Knijn A, Marchesi F, Capocaccia R; EUROCare Working Group EUROCare-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. Eur J Cancer. 2009;45(6):931–91.
5. Dubecz A, Gall I, Solymosi N, Schweigert M, Peters JH, Feith M, et al. Temporal trends in long-term survival and cure rates in esophageal cancer: a SEER database analysis. J Thorac Oncol. 2012;7(2):443–7.
6. Lagergren J, Mattsson F. Diverging trends in recent population-based survival rates in oesophageal and gastric cancer. PLoS Onc. 2012;7(7):e41352.
7. Merkow RP, Bilimoria KY, McCarter MD, Chow WB, Gordon HS, Stewart AK, et al. Effect of histologic subtype on treatment and outcomes for esophageal cancer in the United States. Cancer. 2012;118(13):3268–76.
8. Claiborne PM, Fowler CS, Vaporiyan AA. Follow-up of patients with resected thoracic malignancies. Thorac Surg Clin. 2012;22(1):123–31 viii.
9. Beuscart JB, Pagniez D, Boulanger E, Lessore de Sainte Foy C, Salleron J, Frimat L, et al. Overestimation of the probability of death on peritoneal dialysis by the Kaplan-Meier method: advantages of a competing risks approach. BMC Nephrol. 2012;13:31.
10. Pintilie M. An introduction to competing risks analysis. Rev Esp Cardiol. 2011;64(7):599–605 (in Spanish).
11. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. Ann Surg Oncol. 2010;17(7):1721–4.
12. Sobin LH, Compton CC. TNM seventh edition: what’s new, what’s changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. Cancer. 2010;116(22):5336–9.
13. Kalbfleisch J, Prentice R. The Statistical Analysis of Failure Time Data. New York: John Willey and Sons; 1980.
14. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988 Sep;16(3):1141–54.
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. JASA. 1999;94:496–509.
16. Rutegdård M, Shore M, Lu Y, Lagergren P, Lindblad M. Sex differences in the incidence of gastrointestinal adenocarcinoma in Sweden 1970–2006. Eur J Cancer. 2010;46(6):1093–100.
17. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013;19(34):5598–606.
18. Cook MB, Dawsey SM, Freedman ND, Inskip PD, Withner SM, Quaishi SM, et al. Sex disparities in cancer incidence by period and age. Cancer Epidemiol Biomarkers Prev. 2009;18(4):1174–82.
19. Bus P, Lemmens VE, van Oijen MG, Creemers GJ, Nieuwenhuijzen GA, van Baal JW, et al. Prognostic factors for medium- and long-term survival of esophageal cancer patients in the Netherlands. J Surg Oncol. 2014;109(5):465–71.
20. Mirnezhad SK, Somi MH, Jangjoo AG, Seyednezhad F, Dastgiri S, Mohammadzadeh M, et al. Survival rate and prognostic factors of esophageal cancer in east Azerbaijan province, North-west of Iran. Asian Pac J Cancer Prev.
21. Liu SZ, Wang B, Zhang F, Chen Q, Yu L, Cheng LP, et al. Incidence, survival and prevalence of esophageal and gastric cancer in Linzhou city from 2003 to 2009. Asian Pac J Cancer Prev. 2013;14(10):6031–4.

22. Sreedharan A, Harris K, Crellin A, Forman D, Everett SM. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev. 2009;(4):CD005048.

23. Bujanda L, Gil I, Sarasqueta C, Hijona E, Cosme A, Elorza JL, et al. Clinicopathological characteristics and survival outcome of esophageal cancer. Results from a series of 200 patients. Med Clin (Barc). 2009;133(18):689–93 (in Spanish).

24. Koppert LB, Lemmens VE, Coebergh JW, Steyerberg EW, Wijnhoven BP, Tilanus HW, et al. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer. Br J Surg. 2012;99(12):1693–700.

25. Bashash M, Shah A, Hislop G, Brooks-Wilson A, Le N, Bajdik C. Incidence and survival for gastric and esophageal cancer diagnosed in British Columbia, 1990 to 1999. Can J Gastroenterol. 2008;22(2):143–8.

26. Coupland VH, Allum W, Blazeby JM, Mendall MA, Hardwick RH, Linklater KM, et al. Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. BMC Cancer. 2012;12:11.

27. Bossard N, Velten M, Remontet L, Belot A, Maarouf N, Bouvier AM, et al. Survival of cancer patients in France: a population-based study from The Association of the French Cancer Registries (FRANCIM). Eur J Cancer. 2007;43(1):149–60.

28. Chen M, Huang J, Zhu Z, Zhang J, Li K. Systematic review and meta-analysis of tumor biomarkers in predicting prognosis in esophageal cancer. BMC Cancer. 2013;13:539.

29. Tachezy M, Effenberger K, Zander H, Minner S, Gebauer F, Vashist YK, et al. ALCAM (CD166) expression and serum levels are markers for poor survival of esophageal cancer patients. Int J Cancer. 2012;131(2):396–405.

30. Bergquist H, Johnsson A, Hammerlid E, Wenger U, Lundell L, Ruth M. Factors predicting survival in patients with advanced oesophageal cancer: a prospective multicentre evaluation. Aliment Pharmacol Ther. 2008;27(5):385–95.

31. Kim T, Grobmyer SR, Smith R, Ben-David K, Ang D, Vogel SB, et al. Esophageal cancer—the five year survivors. J Surg Oncol. 2011;103(2):179–83.

32. Veisani Y, Delpisheh A, Sayehmiri K, Rahimi E. Demographic and histological predictors of survival in patients with gastric and esophageal carcinoma. Iran Red Crescent Med J. 2013;15(7):547–53.

33. National Comprehensive Cancer Network. Clinical Practical Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers (excluding the proximal 5 cm of the stomach). Version 2. 2013.

34. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449–72.

35. Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D; ESMO Guidelines Working Group. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:v151–6.