Cancer Epidemiology 37 (2013) 91–96

Contents lists available at SciVerse ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Factors involved in health-related transitions after curative resection for pancreatic cancer. 10-Years experience: A multi state model

A. Álvaro-Meca [a,*], R. Akerkar [b,1], M. Alvarez-Bartolome [c], R. Gil-Prieto [a,2], H. Rue [b,3], Á. Gil de Miguel [a,4]

[a] Department of Preventive Medicine & Public Health, Rey Juan Carlos University, Madrid, Spain
[b] Department of Mathematical Sciences, Norwegian University of Science and Technology, Norway
[c] Ministry of Health and Social Policity, Spain

ARTICLE INFO

Article history:
Received 23 December 2011
Received in revised form 1 September 2012
Accepted 8 September 2012
Available online 29 September 2012

Keywords:
In hospital mortality
Multi state model
Pancreatic cancer
Pancreatic resection

ABSTRACT

Background: Pancreatic cancer is one of the least common tumours, nevertheless it is one of the most lethal. This lethality is mainly due to the fact that the vast majority of patients are diagnosed in an advanced stage. The purpose of this study was to investigate how different covariates affect the transition to death or discharge with and without complications after pancreatic resection. *Methods*: We analyse the impact of different factors on transitions after pancreatic resection based on a multi state model. *Results*: Transitions of interest include the transition to death/discharge with/without complications after pancreatic resection. We consider presence of comorbidities, higher age (>60), gender-male, lower hospital volume (<10 cases per year), type of surgery, localization of tumour and transfusion received as covariates with a potentially negative effect on the transition intensities to death with or without complications. *Conclusions*: The multi-state model allows for a very detailed analysis of the impact of covariates on each transition, since effects of covariates may change depending on the current state of the patient, thus helping surgeons and patients throughout the surgical process and counselling patients if needed.

1. Introduction

In Europe, pancreatic cancer is the 10th most common cancer, accounting for some 2.6% of all cancers in both sexes [1]. It is the deadliest solid cancer and currently the fourth leading cause of cancer-related deaths [2]. This lethality is mainly due to the fact that the vast majority of patients are diagnosed in an advanced stage. Unfortunately, due to the late presentation of symptoms, only 10% to 20% of patients are candidates for surgical resection, which remains the only viable option for curing the disease [3]. Findings from multiple studies [4] suggest that major pancreatic resection can be performed with an operative mortality of 5% or less. This reduction has been attributed to a variety of advances in preoperative evaluation, surgical techniques and postoperative care, which have reduced surgical morbidity and mortality related to pancreatic surgery [5]. However, the decrease in procedure-related mortality cannot be the sole explanation for the increase in 5-year survival from less than 5% to greater than 20% [3]. In an effort to seek explanations for the improvement in survival rates, several studies analysed the determinants of long-term survival in post-resection pancreatic cancer patients. The covariates found to be associated with survival outcomes include demographics and perioperative and histopathologic covariates. However, there is some controversy with these covariates because many of these studies are limited to small institutions [3] and only take into account one possible outcome (death or discharge alive), thus not considering other possible states that can exist, such as death with and without complications or discharge with and without complications. The importance of different covariates may vary depending on the current state of the patient. For this reason, multiple transitions between states of interest can be studied in multi-state models that rely on regression specifications for transition intensities, by analogy with the well-known Cox model for survival analysis. Multi-state models have been applied to different fields such as cancer [6], nosocomial infections [7] and sleep disorders [8], among many other applications. Their main advantage is that they allow one to analyse the impact of

* Corresponding author at: Department of Preventive Medicine & Public Health and Medical Immunology & Microbiology, Rey Juan Carlos University, Avd Atenas S/N, 28922 Alcorcón, Madrid, Spain. Tel.: +34 91488 8673.
E-mail addresses: alejandro.alvaro@urjc.es (A. Álvaro-Meca), akerkar@math.ntnu.no (R. Akerkar), malvarezb@mspsi.es (M. Alvarez-Bartolome), ruth.gil@urjc.es (R. Gil-Prieto), Havard.Rue@math.ntnu.no (H. Rue), angel.gil@urjc.es (A.G. de Miguel).
[1] Tel.: +47 7359 2021.
[2] Tel.: +34 91488 8625.
[3] Tel.: +47 7359 3533.
[4] Tel.: +34 91488 8847.

1877-7821/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.canep.2012.09.001

covariates on each transition in the model separately. In this paper we employ a Bayesian semi-parametric multi-state model [9] to investigate how different covariates affected the transition to death/discharge after post-resection of pancreatic cancer patients between 1999 and 2009.

2. Materials and methods

2.1. Patients

Hospital discharge data related to pancreatic cancer were extracted from the Minimum Basic Data Set (MBDS), the Spanish hospitalization data collection system, with a total of 38,207,958 hospitalizations between 1999 and 2009. Following Teh et al. [4], a case was included in the study for analysis if it had any of the following diagnosis codes: 157.0–157.2. The procedure codes used were partial pancreatectomy (codes 52.51, 52.52 and 52.59) and total pancreatectomy (codes 52.53, 52.6 and 52.7). We selected all cases that had one of these diagnosis codes and one of these procedure codes. Finally, we selected 5056 patients registered between January 1, 1999 and December 31, 2009. In this period, 274 hospitals performed 15,092 pancreatectomies. We classified these hospitals into 3 groups based on terciles of volume of pancreatectomies per year, following Bilimoria et al. [10]: hospitals with fewer than 9 surgeries, between 9 and 19 and more than 19 surgeries per year. If a patient had more than one admission, only the first admission was considered. Comorbidities identified for this study were based on the Elixhauser index [11]. The postoperative complications were based on guidelines in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Following Teh et al. [4], we established 6 different categories of complications: Cerebrovascular (codes 430–432, 434.00, 434.01, 434.10, 434.11 and 436), Pulmonary (codes 415.1, 481–482 and 485–486), Cardiovascular (codes 410 and 427), Renal (code 574), Lower Extremity (codes 451.1, 451.19 and 451.20), and Wound Infection (code 998.59). Mortality without complications was defined as in-hospital mortality after a pancreatic resection without the presence of one of these complications. Mortality with complications was defined as in-hospital mortality after pancreatic resection with one or more complications. In a similar way, we defined discharge alive without complications and with complications following the same criteria. We analysed two types of covariates: demographic covariates (such as age, gender, comorbidity and year of resection) and perioperative covariates such as type of resection with localization of tumour (partial pancreatectomy in head of pancreas, partial pancreatectomy in body or tail of pancreas and total resection of pancreas), transfusion received (codes V58.2, 99.00–99.09) and hospital volume.

2.2. Statistical analysis

In our application, we take into account five states depicted in Fig. 1. Here, at any point in time, a subject occupies one of the five states corresponding to the following:

1. *Pancreatic resection*: Admission with a pancreatic resection.
2. *Discharge without complications*: Discharge alive without complications after pancreatic resection.
3. *Discharge with complications*: Discharge alive with complications after pancreatic resection.
4. *Death without complications*: In-hospital death without complications after pancreatic resection.
5. *Death with complications*: In-hospital death with complications after pancreatic resection.

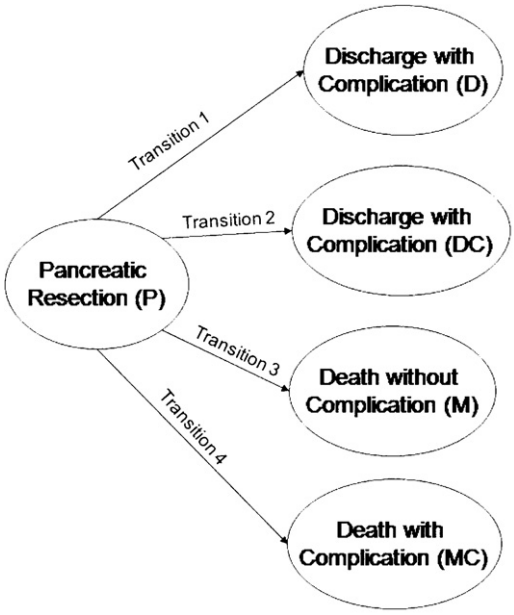

Fig. 1. Different transitions between states.

We considered a semi-parametric Bayesian multi-state model in determining the effect of the different covariates on each of the transitions indicated in Fig. 1. We included information about the selected covariates in a multi-state model in order to validate the hypothesis that different covariates show different impacts on the transitions between the states. A multi-state model is characterized by a collection of hazard rates $\lambda_{hi}(t)$, where h indicates the type of transition and $i = 1, \ldots, n$, indicates a specific observation (see [9]). Because the hazard rates are related to the duration between transitions, we specify regression models by analogy with hazard-rate models for continuous time survival analysis. More specifically, $\lambda_{hi}(t)$ is modelled using a multiplicative Cox-type method as

$$\lambda_{hi} = \exp(\eta_{hi}(t))$$

where $\eta_{hi}(t)$ is a time-dependent, transition-specific regression predictor. We chose the following specifications for the four transitions in our model:

$$\lambda_{12,i}(t) = \exp\left[g_0^{12}(t) + f_{\text{year}}^{12}(y_i) + x_i'\gamma^{12}\right]$$
$$\lambda_{13,i}(t) = \exp\left[g_0^{13}(t) + f_{\text{year}}^{13}(y_i) + x_i'\gamma^{13}\right]$$
$$\lambda_{14,i}(t) = \exp\left[g_0^{14}(t) + f_{\text{year}}^{14}(y_i) + x_i'\gamma^{14}\right]$$
$$\lambda_{15,i}(t) = \exp\left[g_0^{15}(t) + f_{\text{year}}^{15}(y_i) + x_i'\gamma^{15}\right]$$

Each transition is related to three effects. A log baseline effect $g_0^h(t)$ describes the temporal variation in the transition intensities common to all observations. $f_{\text{year}(y)}^h$ represents possible nonlinear effects of time y. Some further parametric covariate effects are collected in the vector x and coefficient γ^h. In our model, these covariates are given by age, sex, comorbidity Elixhauser index, hospital volume, type of surgery with localization of tumour, year of resection and need for transfusion. Note that all effects are transition-specific, and we are particularly interested in differences between covariate effects across intensities. We avoided parametric assumptions about the log baseline effect $g_0^h(t)$ and modelled it using a piecewise constant function. The nonlinear effect of time $f_{\text{year}(y)}^h$ is modelled as a smooth function. Moreover,