Survival Analysis of Cancer Patients in Portugal following the Reference Centre Model Implementation

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Abstract

Cancer has a globally high incidence, having affected around eighteen million people all over the world in 2018. According to the World Health Organization, this figure is expected to nearly double by 2040. In Portugal, cancer was diagnosed in sixty thousand individuals during 2018, being the second leading cause of death in that year, associated with one in every four deaths. Following the publication of the European Directive 2011/24/EU, the Portuguese Health System has been officially recognizing highly specialized clinical centres – Reference Centres, focused on delivering best-in-class treatment for specific health conditions, including cancer. This paper performs a survival analysis on data for cancer patients with discharge date between 2010 and 2019 in Portugal, from a set of six cancer types which have seen the creation of Reference Centres: hepatobiliary, pancreatic, sarcomas, oesophageal, onco-ophthalmology and testicular oncology. The aim is to assess the impact of RCs on the survival probability of these patients. Each group of patients, per cancer type, is subject to a methodology developed according to the best practices described in the literature: a descriptive analysis is made, survival curves are estimated using the Kaplan-Meier methodology, and hazard ratios are estimated for different covariates, using multivariate Extended Cox models. The results obtained support the implementation and encourage the further extension of the RC model for oncology in Portugal, as the cancer patients treated in an oncology RC, overall, have a better survival probability when compared to patients who had no episode in a RC. These results are clearer for hepatobiliary and pancreatic cancer, but also visible for sarcomas and oesophageal cancer. Regarding onco-ophthalmology and testicular cancer, due to the relatively low number of patients and deaths registered, no conclusive results were obtained.

Keywords: Reference Centre, Cancer Survival Analysis, Kaplan-Meier Method, Extended Cox Models

1. Introduction

Over the last years, Portugal has seen a remarkable improvement in terms of health care services provided to patients, reflected on general health indicators, such as life expectancy at birth. Nevertheless, the Portuguese Health System, like other health systems in Europe, is increasingly faced with new challenges. The ageing of the population is one of those challenges, which has been driving a growing number of cancer cases year over year, up to a rate of approximately 3% [1]. Cancer is the leading cause of death in Portugal before the age of 70 and the second cause of death for all ages nationwide [2]. According to the International Agency for Research on Cancer, there have been approximately 58.000 new cases and 29.000 deaths from cancer in Portugal, during the year 2018 [3]. The cancer diagnosis and treatment are also complex and have relevant associated costs. In particular for Portugal, Lopes et al. [4] have estimated cancer treatment to account for an annual cost of 867 million euros in 2017, related to direct medical costs, representing 5.5% of Portuguese total health expenditure.

Following the publication of the European Directive 2011/24/EU in 2011, which is centred on promoting patients' rights in cross-border healthcare, the Portuguese Ministry of Health has created a Work Group, focused on pushing forward the definition of Reference Centre (RC), to be incorporated in the European Reference Networks. This Group has published a final report which defines a RC "*as a unit providing healthcare, with verified technical knowledge on the administration of high quality health care to patients in certain clinical situations, which require resources on a large scale, as well as knowledge and expertise, due to the low prevalence rate of a condition, and how complex the diagnostic or treatment procedures are and the high costs of these same situations*" [2, p. 5]. This Work Group has defined a set of priority areas to be considered for RC creation, among which oncology, due to the traditionally high complexity and costs associated,

but also the need for multi-disciplinary teams and technological equipment [2].

The first oncology RC was officially recognized in Portugal in 2015, reaching a total of fifty RCs as of today. Taking into account the high mortality associated to cancer, but also the objectives for RCs to provide high-quality health care, this paper aims to present a survival analysis, comparing cancer patients who had at least one episode (i.e., have been "referred") or all episodes in a RC, to patients who had no hospital episode in a RC.

The rest of the paper is organized as follows: section 2 presents an overview of the literature regarding survival analysis; In section 3, the data and methodology used for the survival analysis are described; section 4 presents the results obtained. Section 5 discusses implications for Public Health Policy. Finally, section 6 presents the conclusions and suggestions for future work.

2. Literature

Survival analysis is a longitudinal statistical method used to study the occurrence and timing of a specific event. The event is usually referred to as failure because it is often related to a negative event, such as death or disease progression [5]. The time variable is referred as the survival time, as it gives the time which the individual has resisted without experiencing the event [5]. Censoring is an analytical problem which occurs in survival analysis when there is incomplete information about an individual, for a follow-up-period, as the survival time is unknown (e.g. the patient does not experience the event - e.g. death, before the end of the study) [5]. Although there is no information about the exact survival time for censored observations, the information up to the time of censoring can still be used for survival analysis [5].

In this paper, two different survival analysis methods were used: the Kaplan-Meier (KM) to obtain and compare survival curves for different study groups; Extended Cox Models, to develop an adjusted multivariate analysis and obtain Hazard Ratios (HRs) for the different covariates (either time-dependent and time-independent).

There are several studies in the literature focused on obtaining survival analysis for cancer patients using KM and Cox models. For example, Wahutu et al. [6] developed a prospective survival analysis including a total of 6291 pancreatic cancer patients living in Oklahoma, United States, between 1997 and 2012. The authors obtained survival curves using the KM method; the difference between survival curves was tested using the log-rank method; HRs were obtained using Cox Models. The results showed improvement in survival time for pancreatic cancer patients in Oklahoma.

Blay et al. [7] studied the impact in terms of relapse and overall survival for sarcoma patients who undergo surgery in a RC. The survival analysis included a total of 29497 patients with sarcoma, from a French network of 26 sarcoma RCs, with an initial diagnosis from 1st January of 2010 to 1st of May 2018. The authors obtained survival curves using KM and developed a multivariate analysis using Cox Models. The results of this study allowed to conclude that when surgery is made in a RC the survival of patients improves [7]. On the other hand, when patients have surgery in a non-RC, re-surgery is two and a half times more frequent than in patients who had the initial surgery in a RC [7].

Sant et al. [8] developed a survival analysis with 954 patients diagnosed with retinoblastoma between 1978 and 1989, recruited from 17 European countries. The authors obtained survival curves using the KM method and Cox models to estimate the impact of different prognostic factors, such as age at diagnosis and sex. The results showed that, although there was some inter-country variance among countries in Europe, overall survival exceeded 90% in most of them [8]. The results of the study also showed an increase in survival, which the authors believe to be related with an increased efficacy of therapies during the period under analysis [8].

3. Data and Methodology

This chapter describes in a first sub-section the data which served as the basis for the analysis in this paper; afterwards, a second sub-section presents the methodology for implementing the survival analysis to the described data.

3.1 Data

Data used in this analysis was provided by ACSS ("*Administração Central do Sistema de Saúde, I.P.*") and includes information about patients with a primary diagnosis associated with one of the following six cancer types: hepatobiliary, pancreatic, sarcomas, oesophageal, onco-ophthalmology and testicular. It includes all the hospital episodes from these patients with discharge dates between the 1st of January 2010 and 25th of November of 2019, in Portugal (the cut-off date corresponds to the moment the data was made available). Each cancer dataset was extracted from the Portuguese Diagnosis Related Groups (DRG) Database.

The dependent variable includes the information about the waiting time (i.e., survival time) until the occurrence of the event of interest (i.e., death).

Some observations are censored since the event did not occur during the follow-up time.

The predictor variables believed to influence the survival of cancer patients are: a) sex of the patient; b) age at diagnosis - the patient's age, in years, on the first registered episode, which is assumed to be the episode in which the cancer diagnosis occurs; c) cumulative number of surgeries – the number of surgeries the patient had up to the moment in analysis; d) cumulative number of infections – the number of infections the patient had up to the moment in analysis; e) cumulative length of stay – the cumulative length of stay in days, up to the moment in analysis; f) severity – the severity attributed to each hospital episode, which can take the following values: 1 – Minor severity; 2 – Moderate severity; 3 – Major severity and 4 – Extreme severity. Furthermore, two additional predictors were considered:

a) All episodes in RC – binary variable which takes value 0 or 1 (1 if the patient had all episodes in an oncology RC, 0 if the patient had at least one episode in a Non-RC).
b) Referred to RC – binary variable which takes value 0 or 1 (0 up until the moment the patient has the first episode in an oncology RC; 1 from the moment, the patient has the first episode in RC).

3.2 Methodology

The methodology has three main phases, which are shown in Figure 1. This phased methodology was applied recursively to each cancer type.

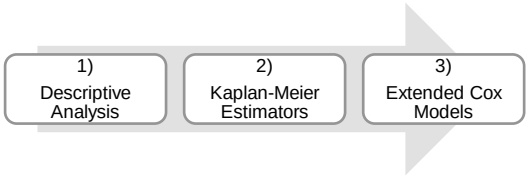

Figure 1 - Methodology overview

The Descriptive Analysis presents the most relevant values obtained from the analysis of each cancer dataset, such as the number of patients, number of episodes, number of male and female patients, number of patients dead and censored during the follow-up period, but also the number of patients who had no episode in a RC, were referred (had at least one episode) to a RC, or had all episodes in a RC.

The second phase is focused on obtaining Kaplan-Meier (KM) estimators with survival curves for different study groups. The KM method allows to obtain estimators of survival functions, in particular for cases which have missing data (censored observations). The formula for Kaplan-Meier survival probability at failure time t_j is shown on Equation 1, and can be interpreted as the probability of a patient surviving past t_{j-1} multiplied by the conditional probability of the patient surviving past t_j, knowing that he/she survived to at least t_j [5].

Equation 1 - Kaplan-Meier survival probability function

$$\mathcal{S}(t_j) = \mathcal{S}(t_{j-1}) \times \mathcal{P}(T > t_j \mid T \geq t_j)$$

In this phase a KM estimator related with RCs was obtained and is presented for each cancer type (when sufficient information was available). This KM estimator includes three survival curves: a curve for patients who had no episode in a RC, another for patients who were referred to a RC and another for patients who had all episodes in a RC. Data was sub-setted to only consider patients who had their first episode after the recognition of the first oncology RC for their cancer type. To assess if two or more KM curves are statistically equivalent, the log-rank test was used.

Finally, the third phase of the methodology is focused on implementing two Extended Cox Models, to develop a multivariate analysis and obtain HRs for the different covariates (described in the previous section). When there is the need to produce a survival analysis including covariates which can change over time (i.e., are not time-independent – e.g. cumulative number of surgeries and cumulative number of infections), an extended Cox Model shall be used. The formula for the extended Cox Model can be seen in Equation 2 and includes the time-independent covariates X_{p1}, and the time-dependent covariates $X_{p2}(t)$. As in the case of the original Cox model, the extended version also includes the vector of coefficients β = (β1, β2,..., βp) and baseline hazard function $h_0(t)$, which is an unspecified function, deriving from the semi-parametric nature of the model [5].

Equation 2 - Extended Cox Model Formula [5]

$$h(t, X(t)) = h_0(t)\, e^{\sum_{i=1}^{p1} \beta_i X_i + \sum_{j=1}^{p2} \delta_j X_j(t)}$$

Two scenarios have been projected for the two models: the first aims to obtain HRs for patients who had all episodes in a RC, compared to patients who had no episode in a RC; the second aims to compare patients referred to RC to patients who had no episode in a RC up to that moment (have not been "referred").

For the first scenario, Extended Cox Model 1 was implemented, including the covariate of interest "All_Episodes_RC" described in the previous section; for the second scenario, the Extended Cox

Model 2 was implemented, including the covariate of interest “Referred_to_RC”. For the selection and validation of additional covariates (the other predictors described before) to be included in both Extended Cox Models, a stepwise forward selection procedure was implemented. First, a univariate analysis was carried out to find statistically significant covariates (p-value < 0.05). All the statistically significant covariates in the univariate analysis were included in the multivariate models, while the statistically non-significant predictors were discarded. If any of the two predictors related with RCs (“All_Episodes_RC” and “Referred_to_RC”) was found to be statistically non-significant in the univariate analysis, the associated Model 1 or 2 was not implemented, as there is not enough information for the multivariate-adjusted model to statistically compare the results, from a RC impact evaluation point of view.

As described by Stensrud et al. [9], the assumption that the HR remains constant from the beginning of the study until the end of follow-up does not happen in practice for most medical interventions, which empirically is the same for the cancer patients in this study (e.g. the hazard can be influenced by the cumulative number of surgeries, cumulative number of infections, which change over time). Thus, the HRs obtained through the two Extended Cox models shall be seen as a weighted average of the time-varying hazard ratios for each cancer type [9]. Following also the suggestion by Stensrud et al. [9], the Restricted Mean Survival Time (RMST) difference was computed, to support clinical-decision making and to make HRs more understandable to interpret. The RMST indicates the average survival time up to a pre-specified, clinically important time, which in the case of the two implemented models will be the minimum largest observed time on each of the two groups (i.e., last follow-up time common to the two different study groups). The RMST difference describes the gain (if positive) or loss (if negative) in terms of survival time for a group of interest (e.g., patients with all episodes in a RC), compared to a control group (e.g., patients who had no episode in a RC).

Each cancer dataset was cleansed and prepared to be loaded for analysis using the R statistical programming language. To implement this methodology, the “survival”, “survminer” and “ggplot2” R packages were used, allowing to obtain the results which are presented in the next section. To take into account the expected format for implementing the two Models in R, data was prepared to code time-dependent covariates with the R “survival” package, using intervals of time as described in the R vignette by Therneau et al. [10][11].

4. Results

This chapter presents the main results obtained from the application of the described methodology to each of the six cancer type in analysis in this paper.

4.1 Hepatobiliary Cancer

A total of 18865 hepatobiliary cancer patients were analysed, which represent a total of 66561 episodes, with discharge date between the 1st of January of 2010 and 25th November 2019 (corresponding to the day of the last registered episode in the dataset). There are a total of 12882 (68%) male and 5983 (32%) female patients, which is in line with previous studies which report hepatobiliary disease (in particular hepatocellular carcinoma – HCC) to have a higher incidence on males, due to a higher incidence of liver cirrhosis [12]. From the total number of patients, 8662 (46%) died during the follow-up period, while 10203 (54%) were censored. Ever since the official recognition of the first hepatobiliary oncology RC, in 2016, up to the end of the follow-up period, there have been 3451 (49%) patients who had no episode in a RC, 704 (10%) patients who have been referred to a RC and 2933 (41%) patients who had all episodes in a RC.

Analysing the KM survival curves related with RCs (Figure 2), the patients who had all episodes in a RC (blue curve) and patients referred to RC (green curve) have higher survival probability at each time than those patients who had no episode in a RC (red curve).

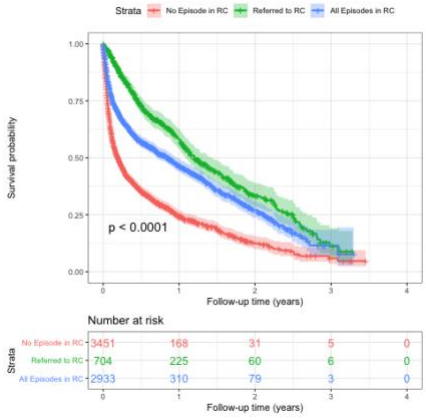

Figure 2 - KM estimators for hepatobiliary cancer patients referred to RC and with all episodes in RC

The main results from the obtained KM estimators for the other predictors have shown that hepatobiliary cancer patients who had one or more surgeries are associated with better survival probability, but also the lower the age of the patient

at diagnosis, the higher the associated survival probability.

Regarding the Extended Cox Models, both "All_Episodes_RC" and "Referred_to_RC" covariates were found to be statistically significant in univariate analysis, as well as all the other covariates ($p < 0.05$).

In Model 1, the patients who had all episodes in a RC have a HR of 0.57 (95% CI 0.52-0.61), indicating a strong relationship between having all episodes in a RC and a decreasing risk of death, when compared to patients who had no episodes in a RC. The patients who have surgeries are also associated with better survival prognosis, having an associated HR of 0.64 (95% CI 0.60-0.68). The computed RMST difference between the patients who had all episodes in a RC (A) and patients who had no episode in a RC (B), for a minimum largest observed time on each of the two groups of 3.302 years (i.e., the minimum of the largest time when death occurred in both groups of patients), is 0.483 years (95% CI 0.385-0.581, with $p < 0.05$), meaning the patients in Group A, on average, live approximately additional 176 days (0.483 years) than patients in Group B.

In Model 2, the patients who have been referred to a RC (Referred_to_RC = 1) have a HR of 0.65 (95% CI 0.57-0.74), indicating a strong relationship between being referred to a RC and a decreasing risk of death, when compared to patients who had no episodes in a RC. The computed RMST difference between the patients who have been referred to a RC (C) and patients who had no episode in a RC (B), for a minimum largest observed time on each of the two groups of 3.283 years, is 0.763 years (95% CI 0.642-0.883, with $p < 0.05$), meaning the patients in Group C, on average, live approximately an additional 279 additional days (0.763 years) that patients in Group B.

4.2 Pancreatic Cancer

A total of 14932 pancreatic cancer patients were analysed, representing a total of 80883 episodes, with discharge date between the 1st of January of 2010 and 22nd November 2019 (corresponding to the day of the last registered episode in the dataset). There are a total of 8077 (54%) male and 6855 (46%) female pancreatic cancer patients. From the total number of patients, 7274 (49%) died during the follow-up period, while 7658 (51%) were censored. The median follow-up time for censored patients is 31 days (ranging from 0 to 3502 days), while the median time of death is 40 days (ranging from 0 to 2896 days). Ever since the official recognition of the first pancreatic oncology RC, there have been 3226 (55%) patients who had no episode in a RC, 478 (8%) patients who had been referred to a RC and 2174 (37%) patients who had all episodes in an RC.

Similarly to hepatobiliary cancer, the main results from the obtained KM estimators have shown that the pancreatic cancer patients who had one or more surgeries are associated with better survival probability, but also the lower the age of the patient at diagnosis, the higher the survival probability. Analysing Figure 3, the patients who had all episodes in a RC (blue curve) or who were referred to a RC (green curve), have a more favourable survival probability at each time than those patients who had no episodes in a RC (red curve).

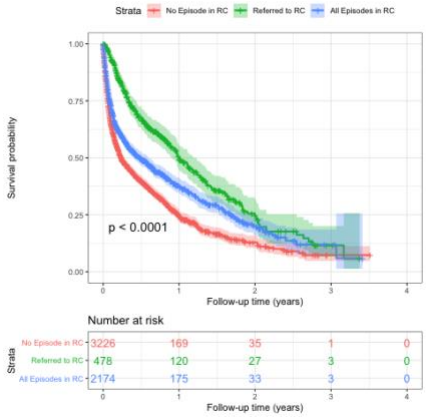

Figure 3 - KM estimators for pancreatic cancer patients referred to RC and with all episodes in RC

For later stages in the follow-up period, the 95% confidence intervals are wider (denoted by the lower and upper bounds around the solid line), due to the higher number of censored patients and lower number of patients at risk. Similarly, the patients referred to RC appear to have a more favourable survival function than the patients who had all episodes in a RC, which can be related to differences in other covariates, such as the severity of the hospital episodes for patients in each group.

Regarding the Extended Cox Models, all predictors were found to be statistically significant ($p < 0.05$) in univariate analysis, except sex ($p = 0.92$), which was not considered for the two Extended Cox Models.

Analysing the results for Model 1, all the included covariates were found to be statistically significant in the multivariate analysis ($p < 0.05$), except the number of infections and length of stay. The patients who had all episodes in a RC have a HR of 0.74 (95% CI 0.68-0.81) being thus associated with reduced risk of death when compared to patients who had no episodes in a RC. The number of surgeries has an HR of 0.66 (95% CI 0.62-0.70), indicating a strong relationship between an increase in the number of surgeries and a reduced risk of death. The computed RMST difference between the

patients who had all episodes in a RC (Group A) and patients who had no episode in a RC (Group B), for a minimum largest observed time on each of the two groups of 3.417 years, is 0.257 years (95% CI 0.145-0.369, with $p < 0.05$), meaning the patients in Group A, on average, live approximately additional 94 days (0.483 years) than patients in Group B.

Analysing the results for Model 2, all covariates were also found to be statically significant in the multivariate analysis ($p < 0.05$), except the number of infections. The HR for pancreatic cancer patients referred to RC is 0.81 (95% CI 0.70-0.94), indicating a better survival prognosis for patients referred to RC, when compared to patients who had no episode in a RC. The number of surgeries has an HR of 0.62 (95% CI 0.57-0.67), indicating also a strong relationship between an increase in the number of surgeries and a reduced risk of death. The computed RMST difference between the patients referred to a RC (Group C) and patients who had no episode in a RC (Group B), for a minimum largest observed time on each of the two groups of 3.379 years, is 0.542 years (95% CI 0.400-0.685, with $p < 0.05$), meaning the patients in Group C, on average, live approximately additional 198 days (0.542 years), than patients in Group B.

4.3 Sarcomas

A total of 6332 sarcomas patients, which represent a total of 31901 episodes, with discharge date between the 1st of January of 2010 and 5th November 2019 (corresponding to the day of the last registered episode in this dataset). There are a total of 3402 (54%) male and 2930 (46%) female sarcoma patients. From the total number of patients, 1154 (18%) died during the follow-up period, while 5178 (82%) were censored. The median follow-up time for censored patients is 13 days (ranging from 0 to 3422 days), while the median time of death is 51 days (ranging from 0 to 2817 days). Ever since the official recognition of the first sarcomas RC, there have been 1036 (53%) patients who had no episode in a RC, 77 (4%) patients who had been referred to a RC and 849 (43%) patients who had all episodes in an RC.

The main results from the obtained KM estimators have shown that the sarcoma patients who had one or more surgeries are associated with better survival probability. The lower the age of the patient at diagnosis, the results have also shown a higher survival probability associated. The KM estimator for length of stay (LOS) have shown that sarcoma patients who have less than 14 days of LOS are associated with better survival probability. Analysing Figure 4, the survival curves for sarcoma patients who had all episodes in a RC (blue curve) or who were referred to a RC (green curve) appear to have a more favourable survival at each time than patients who had no episode in RC (red curve). This is particularly clearer at an early stage of the follow-up period, when there are more patients in the groups at risk (which can be seen in the table below the chart) than at later stages in the follow-up period, when there are fewer patients (there is an increasing number of censored patients).

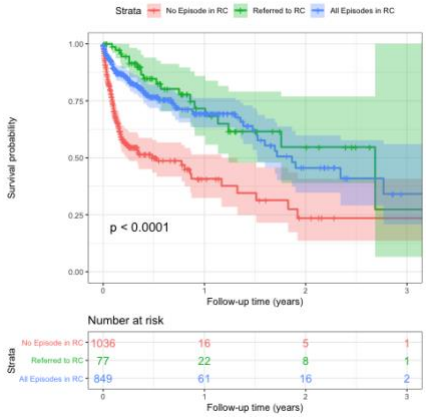

Figure 4 - KM estimators for sarcoma patients referred to RC and with all episodes in RC

Regarding the Extended Cox Models, the univariate analysis for the different predictors has given statistically significant p-value for the covariate "All_Episodes_RC" ($p < 0.05$) and non-significant p-value for the covariate "Referred_to_RC" ($p = 0.64$). Therefore, since each of the models respectively depends on each of these covariates being statistically significant, Model 1 was implemented, while Model 2 was not ($p > 0.05$).

Analysing the results for Model 1, all covariates were found to be statistically significant in the multivariate analysis ($p < 0.05$), except the number of infections and length of stay. The patients who had all episodes in a RC have a HR of 0.60 (95% CI 0.46-0.79), being thus associated with reduced risk of death when compared to patients who had no episodes in a RC. The number of surgeries has an HR of 0.81 (95% CI 0.73-0.89), indicating a relationship between an increase in the number of surgeries and a reduced risk of death. The RMST difference between the sarcoma patients who had all episodes in a RC (Group A) and patients who had no episode in a RC (Group B) was computed, for a minimum largest observed time on each of the two groups of 3.261 years, is 0.711 years (95% CI 0.344-1.077, with $p < 0.05$), meaning the patients in Group A, on average, live approximately additional 260 days (0.711 years) than patients in Group B.

4.4 Oesophageal Cancer

A total of 7572 oesophageal cancer patients, which represent a total of 47349 episodes, with discharge date between the 1st of January of 2010 and 25th November 2019 (corresponding to the day of the last registered episode in the dataset). There are a total of 6343 (84%) male and 1229 (16%) female oesophageal cancer patients. This type of cancer affected mainly male patients, which is also aligned with the existing literature regarding sex prevalence. From the total number of patients, 3116 (41%) died during the follow-up period, while 4456 (59%) were censored. The median follow-up time for censored patients is 44 days (ranging from 0 to 3212 days), while the median time of death is 101 days (ranging from 0 to 2935 days). Ever since the official recognition of the first oesophageal oncology RC, there have been 1410 (55%) patients who had no episode in a RC, 253 (10%) patients who had been referred to a RC and 884 (35%) patients who had all episodes in an RC.

Analysing Figure 5, the survival curves show a more favourable survival probability at an earlier stage of the follow-up period for patients who were referred (green curve) and had all episodes (blue curve) in a RC, than those patients who had no episodes at a RC (red curve).

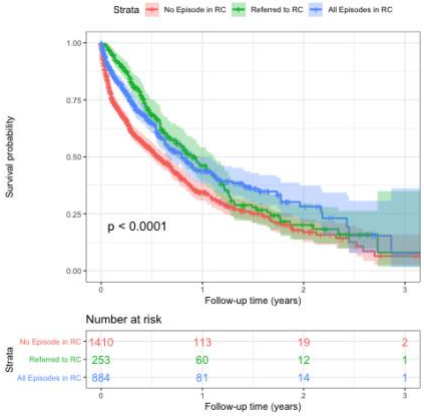

Figure 5 - KM estimators for oesophageal cancer patients referred to RC and all episodes in RC

The main results from the obtained KM survival curves for the other predictors have shown that patients who had one or more surgeries are associated with better survival probability. The KM for length of stay (LOS) have shown that the patients who have less than 14 days of LOS are associated with better survival probability.

Regarding the Extended Cox Models, the univariate analysis has given statistically significant p-value for the covariate "All_Episodes_RC" ($p < 0.05$) and statistically non-significant p-value for the covariate "Referred_to_RC" ($p = 0.63$). Therefore, Model 1 was implemented, with all the covariates ($p < 0.05$), while Model 2 was not, due to the covariate of interest for the second Model not being statistically significant ($p > 0.05$).

Analysing the obtained results for Model 1, all covariates were found to be statistically significant in the multivariate analysis ($p < 0.05$), except sex and number of hospital infections. Regarding the main covariate of interest in this Model, "All_Episodes_RC", the HR is 0.64 (95%CI 0.56-0.75), indicating a strong relationship between having all episodes in a RC and a decreasing risk of death, when compared to patients who have no episode in a RC. The number of surgeries has a HR of 0.87 (95% CI 0.80-0.90), showing a decreasing risk of death with the increase of the number of surgeries, which can be associated with the potential curative aspect of surgery for oesophageal cancer patients. The RMST difference between the oesophageal cancer patients who had all episodes in a RC (Group A) and patients who had no episode in a RC (Group B) was computed, for a minimum largest observed time on each of the two groups of 3.149 years, is 0.237 years (95% CI 0.052-0.4422, with $p < 0.05$), meaning the patients in Group A, on average, live approximately an additional 87 additional days (0.237 years) than patients in Group B.

4.5 Onco-ophthalmology

A total of 277 onco-ophthalmology patients were included in the dataset, corresponding to 697 episodes, with discharge date between the 25th of January of 2010 and 6th November 2019 (corresponding to the day of the last registered episode in the dataset). There are a total of 141 (51%) male and 136 (49%) female onco-ophthalmology patients. From the total number of patients, 31 (11%) died during the follow-up period, while 246 (89%) were censored. The median follow-up time for censored patients is 12 days (ranging from 0 to 711 days), while the median time of death is 4 days (ranging from 0 to 2248 days). For the total follow-up period, there are a total of 266 (~ 95%) patients who had no episode in a RC, a total of 1 (~ 0.3%) patient who was referred to a RC and 10 (~ 4%) patients who had all episodes in a RC. From the total of patients who were referred or had all episodes in an onco-ophthalmology RC (11 patients), all have been censored (i.e., none has died, according to the available data for the follow-up period).

The KM estimators for onco-ophthalmology patients are difficult to interpret as the number of patients is relatively low, but the main results have shown that patients who have one or more surgeries and no hospital infections are associated with better

survival prognosis. Regarding the KM estimator which compare the survival curves of patients who had no episode in a RC, were referred to a RC or had all the episodes in a RC, since there are no deaths recorded for patients in patients who had at least one episode in a RC, the survival probability given for those patients is one for all the follow-up period of time. This makes it difficult to compare the survival curves for these study groups, reason why this KM estimator was not included in this paper.

The application of the two Extended Cox Models, depends on the existence of relevant information in the study groups. In the case of the predictors "Referred_to_RC" and "All_Episodes_RC", there is only one patient who was referred to a RC, and eleven patients who had all episodes in a RC – none of these total eleven patients have died during the follow-up period. Therefore, it was not possible to study and compare the survival and HR for these patients, according to the defined methodology.

4.6 Testicular Cancer

A total of 2260 testicular cancer patients were considered, representing a total of 15014 hospital episodes. These patients had episodes with discharge date between the 1st of January of 2010 and 25th November 2019 (corresponding to the day of the last registered episode in the dataset). For the total of patients, 2162 (95%) were censored, while 107 (5%) have died during the follow-up period. The median follow-up time for censored patients is 28 days (ranging from 0 to 2676 days), while the median time of death is 88 days (ranging from 0 to 3246 days). Ever since the official recognition of the first testicular oncology RC, there have been 543 (66%) patients who had no episode in a RC, 53 (6%) patients who had been referred to a RC and 230 (28%) patients who had all episodes in an RC.

The main results from the KM estimators have shown that testicular cancer patients who have one or more surgeries and who are younger at diagnosis (less than 40 years old) are associated with better survival probability. Figure 6 shows the KM estimator with survival curves for patients who had all episodes in a RC, patients who were referred to a RC and patients who had no episode in a RC. The results from the application of the log-rank test to this KM estimator gave a statistically non-significant p-value (p = 0.33). Therefore, no conclusion can be obtained regarding the impact of RCs on survival for testicular cancer patients since the survival curves do not differ significantly among them (p > 0.05).

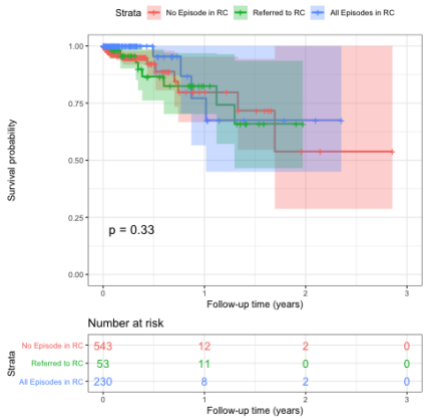

Figure 6 - KM estimator for testicular cancer patients referred to RC and with all episodes in RC

Regarding the Extended Cox Models, the implementation of univariate analysis for each of the covariates of interest has given statistically non-significant p-value for "All_Episodes_RC" (p = 0.15) and statistically significant for "Referred_to_RC" (p = 0.021). All the other covariates were found to be statistically significant (p < 0.05), except the number of surgeries and severity. Therefore, only Model 2 was implemented, including the statistically significant covariates from the univariate analysis.

Analysing the results from Model 2 implementation, although the covariate "Referred_to_RC" was statistically significant in the univariate analysis, with the implementation the Model 2, the covariate "Referred_to_RC" was found to no longer be statistically significant (p = 0.263). Furthermore, the 95% confidence interval is relatively wide (0.59-7.6). Therefore, no statistically significant conclusion can be drawn out from the implementation of this model, regarding the impact on survival for testicular cancer patients referred to RCs, when adjusted to other covariates.

5. Discussion of the results and implications for Public Health Policy

The results obtained using the KM method show survival curves with overall better survival probability, at each moment, for patients who have either been referred or who had all the hospital episodes in a RC, when compared to patients who had no episode in a RC. These conclusions apply for hepatobiliary, pancreatic, oesophageal and sarcomas cancer types, but are more noticeable in the cases of hepatobiliary and pancreatic cancer. For testicular cancer and onco-ophthalmology, similar conclusions were not possible to obtain due to the relatively small number of patients included in the dataset for these cancer types and the high number of censored patients (i.e., patients who did not die during the follow-up period). Comparing the survival curves of patients who were referred to a

RC and patients who had all episodes in a RC, the former appear to have better survival probability at each time when compared to the latter. Since the KM methodology produces a univariate analysis (i.e. does not consider other covariates, such as severity or number of surgeries), these results may be ignoring the effect of other variables, which can affect survival and be different between the two study groups.

Hence, a multivariate analysis using two Extended Cox Models was performed. The results obtained from the two Models for hepatobiliary and pancreatic cancer have shown a better survival outlook for patients who either had all episodes in a RC (Model 1) and who had at least one episode in a RC (Model 2), when compared to patients who had none episode in a RC. Comparing the results obtained from Models 1 and 2 for hepatobiliary and pancreatic cancer, patients who had all episodes in a RC seem to have better survival prognosis than patients who were referred to a RC, as there is a lower HR for the first group of patients, when compared with the reference group of patients who had no episode in a RC (patients who had no episode in a RC in Model 1 and patients who had no episode in a RC – i.e. had not been referred, up to that moment in Model 2). These results allow to conclude that other covariates (e.g. severity, number of surgeries) may affect overall hepatobiliary and pancreatic cancer patients' survival prognosis, which can explain the difference obtained using the KM method.

For the case of sarcomas and oesophagus cancer, only the Extended Cox Model 1 was implemented, as no statistical significance was found for the covariate of interest of Model 2 ("Referred_to_RC"). The results of Model 1 have shown, for both sarcomas and oesophagus cancer, that patients who had all episodes in a RC have better survival prognosis than patients who had no episode in a RC.

For the cases of onco-ophthalmology and testicular cancer, Models 1 and 2 were not implemented as no statistical significance was obtained beforehand in the univariate analysis for the covariates of interest ("All_Episodes_RC" and "Referred_to_RC"). This can be related with the relatively small number of patients, as well as with the low mortality, when compared to other cancer types. A similar challenge was found in the survival analysis study of retinoblastoma (related with onco-ophthalmology) developed by Sant et al. [8] – due to low incidence of retinoblastoma and the need for a high number of cases to allow to obtain a reliable survival analysis, data was collected from 28 European population-based cancer registries. In future survival analysis of onco-ophthalmology and testicular cancer, due to their low incidence and relatively low mortality, one possible approach may be similar to the one adopted by Sant et al. [8].

Table 1 presents the cancer types analysed in this paper, displaying information about the number of RC's and the percentage of patients who were not referred to a RC (i.e., percentage of patients who had no episode in a RC). This table does not include information for other cancer types with existing oncology RCs in Portugal, such as rectum oncology and paediatric oncology RCs, as those were not analysed in this paper. There are still close to half or more cancer patients who had no hospital episode in an oncology RC. Since survival probability can improve for patients referred to a RC, one should look for the reasons why these patients are not being referred (e.g., lack of accessibility for patients who live far away from a RC) and propose solutions, from a health management perspective, to increase their accessibility to RCs.

Table 1 – Percentage of cancer patients not referred to RC

Cancer Type	% of patients not referred to RC
Hepatobiliary	49%
Pancreatic	55%
Sarcomas	53%
Oesophagus	55%
Onco-ophthalmology	62%
Testicular	66%

According to the Portuguese National Programme for Oncologic Disease [13], one of the goals for 2020 is to ensure that 75% of the rectum, pancreatic and testicular cancer patients are treated in a RC. Taking into account the results obtained in this paper, the extension of this goal to other cancer types is expected to promote better survival probability for cancer patients, in particular for hepatobiliary cancer, but also for sarcomas and oesophagus cancer patients. Nevertheless, there is still a relevant percentage of these patients who need to be referred to a RC (as can be seen in Table 1). Therefore, an important effort is expected to achieve this goal.

An immediate consequence of the results presented in this paper, in terms of public health policy, is thus the need to improve the network of RCs, as well as patients' access to the services they provide. This can be achieved through investment towards forming and recognizing new oncology RCs, but also by enhancing the referring of cancer patients to existing RCs. A possible strategy to promote the referral of cancer patients can be the recognition of oncology Affiliate Centres (i.e., centres which do not meet all criteria to be recognised as RC, but nevertheless have knowledge and competency in oncology). These Affiliate Centres shall establish

close relationships with RCs, to promote and enhance referral pathways for cancer patients.

The annual costs of cancer treatment in Portugal, associated with direct medical costs, account to 867 million euros, representing 5.5% of Portuguese health expenditure. In addition to contributing to a better survival prognosis for patients, the implementation and promotion of the RC Model can support the achievement of economies of scale and allow to take advantage of the scope and experience economies provided by RCs, which is one of the main objectives for the RC model implementation, as described by Penedo et al. [2]. In addition to contributing to a better quality of life for these patients, such a measure may thus also save money by increasing the efficiency of the treatments and reducing average costs.

6. Conclusions and future work

The main conclusion presented in this paper is that, overall, cancer patients who are treated in a RC (at least one or more hospital episodes) present better survival probability at each moment than patients who had no hospital episode in a RC. This is clearer for hepatobiliary and pancreatic cancer patients, but also visible in the case of sarcomas and oesophageal cancer patients (although with wider confidence intervals). In the case of hepatobiliary and pancreatic cancer, the two multivariate models, adjusted for other covariates (e.g., mean severity of the patient, number of surgeries, number of infections, etc.), show a better survival prognosis for patients who had all episodes in a RC than for patients who were referred to a RC. In the case of sarcomas and oesophageal cancer, the benefits in terms of survival are also visible in the KM results. For onco-ophthalmology and testicular cancer, due to the relatively small number of patients annually treated in Portugal, it was more difficult to obtain accurate conclusions in terms of survival. This can be related to the relatively low number of patients recorded as dead during the follow-up period, and high number of censored patients.

The conclusions support the RCs Model implementation for oncology, as the collected data indicates a positive impact in terms of survival for cancer patients who have been referred or had all episodes in a RC, when compared to patients who had no episodes in a RC. This conclusion is also aligned with the literature for the implementation of the RC Model in different countries [7][14][15][16].

A possible future area of research can be the study of the impact on survival for patients treated in RCs with more years of experience – the expectation is that the treatment in a RC improves over time, with the increase in volume, resources and experience. This research can also be extended to other cancer types in Portugal (e.g. rectum cancer), but also to other health intervention areas which have seen the creation of RCs, such as transplantation of solid organs or interventional cardiology and hemodynamics.

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