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Population-level cure of colorectal cancer in Malta: An analysis of patients diagnosed between 1995 and 2004

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ABSTRACT

Aim: The aim of this study was to estimate the population-level 'cure' of Maltese colorectal cancer patients diagnosed between 1995 and 2004, and to estimate the median survival time for the 'uncured' patients.
Methods and study population: Analysis was conducted on 1470 cases registered by the Malta National Cancer Register between 1995 and 2004 and followed up to end of 2010. The mean age of the patients was 66.4 (95%CI 65.8–67.1), and the number of men and women were equal. Background mortality for 1995–2010 was extracted from publicly available life tables. A mixture model with Weibull survival distribution and identity link was used to model 'cure'.
Results: The overall 'cured' proportion for the patients diagnosed in 1995–1999 was 45.3% (95%CI 40.2–50.5) while the 'cured' proportion for the patients diagnosed in 2000–2004 was 52.3% (95%CI 47.2–57.5). Median survival time for the 'uncured' patients increased in the second calendar period from 1.25 years (95%CI 1.04–1.45) to 1.42 years (95%CI 1.15–1.76).
Conclusion: In Malta, as in the rest of Europe, improvements have been made in short- and long-term survival over the 15-year period under study. To continue this improvement, differences by age that still persist must be investigated and efforts focused to reduce any gaps between Malta and other European countries.

1. Introduction

Cancer is one of the leading causes of death worldwide and colorectal cancer is the fourth most common cause of cancer death. It is estimated that in Europe there were 214,700 deaths from colorectal cancer (12.3% of all cancer deaths) in 2012 [1]. In Malta, in 2013, colorectal cancer was the second leading cause of cancer death amongst both men and women [2].

Relative survival analysis presents survival estimates adjusted for the background risk of death at particular time points after diagnosis. An extension of the relative survival concept is the notion of 'statistical cure' or 'population cure'. This is defined at a group level and is different from the concept of individual cure where patients can be considered medically free of cancer [3]. 'Population cure' relates to the tendency for some cancer relative survival curves to reach a plateau after a period of follow-up. This indicates that the excess mortality attributed to the cancer of the patient is equal to their background mortality, and thus these cancer patients are no more likely to die than their counterparts in the general population. The analysis of 'cure' can expand our understanding of the pattern of cancer survival.

The EUROCARE project estimated the 'cured' proportion of patients diagnosed between 1978 and 1999 in Europe [4,5] and found a 12% improvement in long-term survival for the 'cured' proportion from 36% in 1978–1985 to 48.5% in 1997–1999. The study also showed a strong negative association between age and 'cure'. Studies conducted in Sweden, Finland and North West England have also made use of 'cure' models to assess survival trends for colorectal cancer and have found similar results [6–8].

The aim of this study was to estimate the proportion of Maltese colorectal patients diagnosed between 1995 and 2004 who were statistically 'cured', and to estimate the median survival time for the uncured. This study is the first to apply 'cure' models on data from the Malta National Cancer Register.

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2. Materials and methods

2.1. Data sources

The data used in this study were taken from the Malta National Cancer Register which collects data for all incident cancers in the population resident in Malta and Gozo [9]. Cancer notification is compulsory by the Notification of Cancer Act of 1957 [10]. Data were collected for all patients diagnosed with colorectal cancer from 1995 to 2004 and followed up to the end of 2010. Colorectal cancers are coded by the registry using the International Classification of Diseases for Oncology (ICD-O-2) and codes C18–C20 were included in this study.

Background mortality for the years 1995–2010 were obtained from life tables available publicly from the National Statistics Office. In these tables age is truncated to 85+ up to 1998 and 90+ from 1999 onwards. Since the risk of death increases exponentially after 85 years of age, and because our cancer patients were aged up to 97 at the end of follow-up, it was necessary to impute age- and sex-specific rates of death for the older ages for each of the years of follow-up. The available life tables were thus extended and smoothed up to 100 years of age using the Ewbank four-parameter method [11], separately by year and gender. The standard life Table used to smooth the data was that available for England and Wales from 1998 to 2000, since no reliable standard was available for Malta. To assess the goodness of fit of the derived life tables, the smoothed mortality rates and survival function in each Table were plotted against the observed mortality rates.

2.2. Study population

In total 1496 patients were eligible for analysis in this study. Of these, 25 were excluded because they were diagnosed only at death via death certificate (1.7%). One more case was excluded because region of residence was unknown. In total 1470 cases were examined. For each patient sex, age at diagnosis, date of diagnosis, date of death and region of residence were collected. Age at diagnosis was grouped into four categories: <55, 55–64, 65–74 and 75+ years. Year of diagnosis was collapsed into two broad cohorts: 1995–1999 and 2000–2004. Vital status and date of death are collected by the registry through death certificates and linkage with the National Mortality Register. Since no variables directly measuring socio-economic status were available, region of residence was used as a proxy for socio-economic status. The National Statistics Office (NSO) classifies the Maltese Islands into six broad geographic regions: North Harbour, South Harbour, South East, West, North and Gozo. The North Harbour is the largest region, with 28.9% of the total resident Maltese population living there, while Gozo, Malta's sister island, is the smallest region at 7.5% of the population [12]. Studies on income and living conditions consistently showed differences across region. The South Harbour region exhibits the highest percentage at risk of poverty and the lowest average household income [13].

2.3. Statistical analysis

The relative survival ratio (or relative survival) is a measure of survival from a particular disease of interest (e.g. cancer) in the absence of other causes of death. In our context, relative survival is the ratio of the survival observed among the cancer patients and the survival that would have been expected if they had experienced the same death rates as the general population from which they derive. Relative survival by age group, sex, calendar period of diagnosis and region of residence was estimated using the Ederer II method [14].

Cure models estimate the proportion of patients 'cured' of their cancer, that is, the proportion of patients who experience no long-term disease-related (excess) mortality. These models are appropriate only when it is believed that 'cure' is a reasonable assumption. This can be established by visual inspection of relative survival curves. A mixture model, which assumed a Weibull distribution and an identity link, was used to estimate 'cure'. We used the model estimates to derive (a) the proportion 'cured'; (b) the relative survival curves for both the whole sample and the 'uncured' patients; and (c) the median survival time of the 'uncured'. Estimation of the model parameters was obtained using the maximum likelihood method on individual patient records.

The modeling strategy aimed to develop a parsimonious model to predict 'cure'. Initially, all covariables – as well as an interaction term between age group and year of diagnosis – were included to estimate the 'cure' fraction and two Weibull parameters. The likelihood ratio test was used to assess the number of covariables included in the model. We also tested whether the Weibull shape and scale parameters varied by the covariables included in the final model. In order to assess the fit of the final model, survival curves were derived from the model estimates and were compared graphically to the estimates obtained using the Ederer II method. All analyses were performed using Stata version 11; *strsmix* [15] was used to model cure.

3. Results

The mean age of the patients was 66.4 (95%CI 65.8–67.1). The proportion of men and women was similar in the two periods. Distribution of patients across the six regions reflects the relative population sizes of the regions (Table 1).

Five-year relative survival for the whole study population (1995–2004) was 53.3% (95%CI 50.3–56.3). Survival estimates were similar for men and women and by period of diagnosis. The curves by age group indicated lower survival in the older age groups. Five-year survival amongst those diagnosed at age <55 was 63.3% (95% CI 58–68.2%), while for those diagnosed age 75+ survival was 47.2% (95%CI 41.5–52.9%). Due to small numbers with increasing years of follow-up, relative survival showed wider variability after 11 years of follow-up, especially when subdividing by multiple categories such as region and age group (Fig. 1).

On visual inspection, 'cure' did not appear to have been attained for the oldest age group (75+); this group was therefore excluded from the 'cure' analysis (1054 patients analyzed). Initially all covariables (age group, sex, region and year of diagnosis) were

Table 1
Patient characteristics.

		Year of diagnosis		
		1995–1999 *N* (%)	2000–2004 *N* (%)	Total *N* (%)
Total		658 (45)	812 (55)	1470 (100)
Characteristic	Category			
Age (years)	<55	127 (19)	139 (17)	266 (18)
	55–64	148 (22)	185 (23)	333 (23)
	65–74	195 (30)	260 (32)	455 (31)
	75+	188 (29)	228 (28)	416 (29)
Sex	Male	324 (49)	418 (51)	742 (50)
	Female	334 (51)	394 (49)	728 (50)
Region	North	56 (9)	95 (12)	151 (10)
	North Harbour	222 (34)	279 (34)	501 (34)
	South East	76 (12)	108 (13)	184 (13)
	South Harbour	151 (23)	174 (21)	325 (22)
	West	88 (13)	86 (11)	174 (12)
	Gozo	65 (10)	70 (9)	135 (9)