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Estimating the cure proportion of malignant melanoma, an alternative approach to assess long term survival: A population-based study

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ABSTRACT

Objectives: A large proportion of patients with cutaneous malignant melanoma (CMM) do not experience excess mortality due to their disease. This group of patients is referred to as the cure proportion. Few studies have examined the possibility of cure for CMM. The aim of this study was to estimate the cure proportion of patients with CMM in a Swedish population.
Methods: We undertook a population-based study of 5850 CMM patients in two Swedish health care regions during 1996–2005. We used flexible parametric cure models to estimate cure proportions and median survival times (MSTs) of uncured by stage, sex, age and anatomical site.
Results: Disease stage at diagnosis was the most important factor for the probability of cure, with a cure proportion of approximately 1.0 for stage IA. While the probability of cure decreased with older age, the influence of age was smaller on the MST of uncured. Differences in prognosis between males and females were mainly attributed to differences in cure as opposed to differences in MST of uncured.
Conclusions: This population-based study showed approximately 100% cure among stage IA disease. Almost 50% of patients had stage IA disease and the high cure proportion for this large patient group is reassuring.

1. Introduction

Cutaneous malignant melanoma (CMM) is the most rapidly increasing malignancy in many countries [1]. In Sweden, there has been an increase in incidence of more than 300% since the 1970s. In 2010, malignant melanoma accounted for approximately 5% of all diagnosed cancers in Sweden [2]. Among the white population in the US, age-adjusted melanoma incidence rates almost tripled among males, and more than doubled among females between 1973 and 1997 [3]. In 2008 malignant melanoma accounted for 4.3% of all diagnosed malignancies in the US [4]. Several clinical and histopathological factors are known to influence survival in CMM. Tumour thickness, measured according to Breslow, and ulceration are considered to be the most important prognostic factors for primary localized CMM [5–8]. Other factors of importance include sex, age at diagnosis, and anatomical site [9–12].

There has been an increase in survival of CMM in Sweden over time [13], and the survival is now high, with localized CMM having a 5-year relative survival of around 90% [10]. A large proportion of CMM patients are thus not expected to experience any excess mortality due to their disease. The fraction of patients who do not experience excess deaths, compared to a disease-free general population, is referred to as the cure proportion [14]. This represents a population definition of cure and does not necessarily imply that all patients are medically cured. With improvements in cancer patient survival and increasing possibility of cure, it is of increasing interest to estimate the cure proportion in population-based studies of cancer patient survival [15–20]. To our knowledge, no study to date has estimated the cure proportion of CMM according to the definition described above.

We used data from two Swedish population-based clinical cancer registries to estimate long-term survival for patients with CMM, using cure models. Such models [14,21–23] can be used to estimate the cure proportion as well as the survival function of

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"uncured" patients. The cure proportion provides an estimate of long-term survival, and estimates of the cure proportion together with estimates of the survival of "uncured" can provide additional information to estimates of, for example, the 5-year relative survival alone.

2. Materials and methods

2.1. Study population

Patients with a diagnosis of CMM were identified in the two regional quality registers in the Uppsala–Örebro and Stockholm–Gotland health care regions in Central Sweden. With about four million inhabitants (representing 43% of the total Swedish population), the composition of the population of Central Sweden has a mix of urban and rural inhabitants similar to that of Sweden as a whole. The clinical quality registers for malignant melanoma include prospectively collected information on age, sex, means of diagnosis, tumour site and stage, histopathological parameters, primary treatment and vital status. The completeness of the clinical quality registries for malignant melanoma exceeded 95% during the period under study as assessed by cross linkage to the population-based Swedish Cancer Register [24].

We identified 6419 diagnoses of invasive CMM located on the head/neck, lower extremity, upper extremity or trunk during the years 1996–2005. Since cure is a long-term measure of survival, we required a potential follow-up of at least 5 years. Only the first diagnosed CMM for individuals with multiple primary CMM was included (157 excluded). For patients with two or more independent primary CMMs diagnosed the same day, we included only the most advanced tumour. All records with missing or incomplete stage information were excluded (412 excluded). The final cohort, consisting of 5850 patients, was followed up until death or 31st December 2010. The study was approved by the Institutional Review Board at Karolinska Institutet.

2.2. Relative survival and cure models

Cancer patient survival is often summarized using 5-year relative survival, interpreted as the proportion of patients that would still be alive 5 years after diagnosis if the cancer (and anything directly or indirectly related to the cancer) was the only possible cause of death [25,26]. Relative survival is estimated as the observed survival divided by the expected survival in a disease-free population. The expected survival is obtained from population life tables, stratified by age, sex, calendar year, and even though the population life tables also include individuals with the disease it has been shown that this bias is negligible [27,28]. The mortality analogue of relative survival is the excess mortality rate and is estimated as the difference between the observed mortality and the expected mortality rates. The advantage of using a relative survival approach, as compared to a cause-specific approach, is that cause of death is not needed.

When the mortality among a cancer patient group returns to the same level as in the general population, that is, when the patients no longer experience excess mortality due to the cancer, the patients still alive are considered "statistically cured". The (statistical) cure proportion is defined as the proportion of patients that do not experience excess mortality due to the disease. While this definition does not necessarily imply that the patients are medically cured, it is a population definition of cure since the patients no longer have a higher mortality rate than the general population. Cure models can be used to estimate the cure proportion as well as the survival function of the "uncured". Analysing temporal changes in both these measures of survival gives more detailed insight into changes in cancer patient survival than that obtained by studying relative survival for the whole group [15].

2.3. Modelling approach

A flexible parametric cure model [29,30] was used. The flexible parametric cure model is a special case of a non-mixture cure model [14], but instead of using a specific parametric distribution, restricted cubic splines are used to model the underlying shape of the survival distribution [31–33]. The flexible parametric cure model has been shown to perform better than the mixture [21,22] or non-mixture cure models with a Weibull distribution, when the latter models give biased estimates or do not converge [30]. For cancer sites with a good prognosis the Weibull cure models often do not converge. This was seen in a Norwegian study that applied cure models to 23 cancer sites, where the mixture cure model did not converge for malignant melanoma [20].

For the main analysis, key variables linked to prognosis were included: age at diagnosis, stage, sex and anatomical site. Age was divided into 4 categories (0–30, 31–50, 51–70, 71 and above), representing young patients, patients in lower and upper middle age and elderly patients, respectively. Stage was classified into clinical stage IA, IB, II or III–IV according to the 2002 American Joint Committee on Cancer (AJCC) melanoma classification system [6]. The flexible parametric cure model included the four main effects, non-proportional excess hazards for all effects as well as interaction terms between anatomical site and stage.

The flexible parametric cure model provides separate estimates of the cure proportion (and relative survival of uncured) for each combination of the covariates included in the model. It is therefore not possible to directly compare two levels of a covariate when adjusting for other covariates, e.g. the difference between stage IA and stages III–IV will be different for each age group, anatomical site and sex. To calculate differences in cure proportions, median survival times of uncured and 5-year relative survival ratios (RSR) between the levels of each variable, adjusted for the other variables, we therefore calculated differences between cure proportions, median survival times of uncured and 5-year RSR that were standardized for all the other variables. For example, differences in the cure proportion between the different stages were calculated as differences in the cure proportion for each stage assuming that the distribution of age, sex and site within each stage was the same as in the whole study population.

All analysis was performed using the stpm2 [31] command in Stata 12 (Statacorp, College Station, TX, USA). A more detailed description of the methods and the modelling approach can be found in an appendix.

3. Results

Overall, 46.3% of patients were diagnosed with clinical stage IA tumours and only 4.1% with stages III–IV disease at time of diagnosis (Table 1). The most common age group at diagnosis was 51–70 years, comprising 39.9% of patients. There was a similar proportion of males and females. CMM on the trunk was the most common site, followed by the lower and upper extremities, while CMM of the head/neck was least common. The total amount of follow-up for the 5850 patients was 44,938 years, the median follow-up time was 7.6 years, and 1951 patients died during follow-up. The potential maximum follow-up time was between 5 and 15 years, with a median of 9.7 years.

Figs. 1 and 2 present the predicted cure proportions for males and females, respectively. Disease stage was the most important determinant of cure, with stage IA having a cure proportion of almost 1.0 for all combinations of anatomic sites, age groups and sex. The cure proportion was similar across age groups for stage IA