EUROPEAN JOURNAL OF CANCER 43 (2007) 2467–2478

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: A review

Maria Ramos[a,*], *Magdalena Esteva*[b], *Elena Cabeza*[a], *Carlos Campillo*[c], *Joan Llobera*[b], *Antonio Aguiló*[d]

[a]*Department of Public Health, Balearic Department of Health, Palma, Spain*
[b]*Primary Health Care Research Unit, Primary Health Care Mallorca District, Balearic Health Service, Palma, Spain*
[c]*Balearic Department of Health, Palma, Spain*
[d]*Balearic Islands University, Palma, Spain*

ARTICLE INFO

Article history:
Received 10 August 2007
Accepted 22 August 2007
Available online 10 October 2007

Keywords:
Colorectal neoplams
Survival
Diagnostic delay
Systematic review

ABSTRACT

Background. Early diagnosis of colorectal cancer before the onset of symptoms improves survival. Once symptoms have occurred, however, the effect of delay on survival is unclear. We review here evidence on the relationship of diagnostic and therapeutic delay with survival in colorectal cancer.

Methods. We conducted a systematic of Medline, Embase, Cancerlit and the Cochrane Database of Systematic Reviews to identify publications published between 1962 and 2006 dealing with delay, survival and colon cancer. A meta-analysis was performed based on the calculation of the relative risk (RR) and on a model of random effects.

Results. We identified 40 studies, representing 20,440 patients. Fourteen studies were excluded due to excessively restricted samples (e.g. exclusion of patients with intestinal obstruction, with tumours at stage C or D at the time of diagnosis, or who died 1–3 months after surgery); or because they studied only a portion of the delay. Of the 26 remaining studies, 20 showed no association between delay and survival. In contrast, four studies showed that delay was a factor contributing to better prognosis, and two showed that it contributed to poorer prognosis. There was no association between delay and survival when the colon and rectum were considered separately, when a multivariate analysis was performed, and when the effects of tumour stage and degree of differentiation were taken into account. To perform a meta-analysis, 18 additional studies were excluded, since the published articles did not specify the absolute numbers. In the remaining eight studies, the combined relative risk (RR) of delay was 0.92 (confidence interval (CI) 95%: 0.87–0.97).

Conclusions. The results of the review suggest that there is no association between diagnostic and therapeutic delay and survival in colorectal cancer patients. Colon and rectum should be assessed separately, and it is necessary to adjust for other relevant variables such as tumour stage.

* *Corresponding author*: Tel.: +34 97 1176885.
E-mail address: mramos@dgsanita.caib.es (M. Ramos).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.08.023

1. Introduction

Colorectal cancer (CRC) is the second most frequent malignant tumour in the developed world in either sex. In Europe it is estimated that in the year 2006 there were 412,000 new cases of CRC, with incidence rates of 55.4 per 100,000 in men and 34.6 per 100,000 in women, and that 207,400 people died of this disease (mortality rates, 27.3 per 100,000 in men and 16.6 per 100,000 in women).[1]

The 5-year survival rate of CRC patients in Europe is 52%, although there is considerable variation among countries, with rates for colon tumours ranging from 26% to 56% for men and from 29% to 59% for women, and rates for rectal tumours ranging from 26% to 56% for men and from 28% to 62% for women. These differences in survival have been attributed to the stage and timing of diagnosis and, in some regions, to the quality of medical care.[2]

CRC is diagnosed principally by the presence of clinical signs, since although screening has proven effective, it is still not widespread.[3] Its clinical presentation is often ill-defined and insidious, especially when the tumour is situated in the right colon. The most frequent symptoms are rectorrhagia, changes in frequency of evacuation, abdominal pain, loss of weight, anaemia and intestinal obstruction,[4–8] with obstruction being an indication of poor prognosis.[9–12] Patients with cancer of the rectum tend to present first with rectorrhagias and changes in frequency of evacuation, accompanied by rectal pain or tenesmus, which together have been termed the 'distal cluster'.[13] In contrast, cancers of the colon become apparent through non-specific symptoms such as anaemia, anorexia, abdominal pain and fatigue.[14]

The time between the first symptoms and the diagnosis of a cancer is termed the diagnostic delay, whereas the time between first symptoms and initiation of treatment is termed the therapeutic delay. In general, however, the duration of symptoms is referred to without specifying the end point of the period. The diagnostic and therapeutic delays are complex concepts involving various factors, including the biology of the tumour, the interaction between the tumour and the host, the behaviour of the patient, the conduct of the physician and the operation of the healthcare system. Intuitively, a reduction in the diagnostic or therapeutic delay should be accompanied by an improved survival rate. This has been shown in breast cancer,[15] but it is not so clear in cancers of other parts of the body.[16,17]

In CRC, the effect of delay on survival has been studied since the 1960s. Between 1937 and 1960 there was a decrease in the mean delay of CRC diagnosis, an increase in the rate of tumour removal, a decrease in the number of cases with obstruction, and a substantial improvement in 5-year survival rate[18] .These observations, however, have not been confirmed, with studies showing either no association between delay and survival,[9,19,20] or that longer delay was associated with a better survival rate.[21–24] We have therefore sought to determine whether diagnostic or therapeutic delay influences survival in CRC.

2. Methods

A systematic review of Medline, Cancerlit, Embase and the Cochrane Database of Systematic Reviews was performed using the keywords colorectal neoplasms OR gastrointestinal neoplasms AND early diagnosis OR diagnostic delay OR patient delay OR provider delay OR survival OR prognosis OR time factors. The search covered systematic reviews and original studies published between 1962 and 2006, with traditional reviews, editorials and letters of opinion excluded. A review was considered to be systematic if, at the very least, it described the procedure followed for the identification and selection of articles. A secondary review was performed, using the bibliography of each of the selected articles as a starting point, which identified other studies. We also consulted the option 'related links' of PubMed. Finally, an attempt was made to identify unpublished doctoral theses through specific Spanish databases (Teseo and tdx) or general search engines (Google). All published and unpublished articles in English and Spanish that studied the association between delay and survival were included, whether the delay was the principal variable of the study or just one of the independent variables. The first selection of papers was based on retrieved titles, and afterwards on the abstracts. In the second phase we reviewed the complete texts of all papers dealing with prognosis and colorectal neoplasms. We started the review in November 2004 and completed it in February 2007.

For critical reading, we utilised criteria used to review non-experimental studies[25–28] and those used in other reviews of the same topic[15] (Table 1). Sample size (Criterion 6) was defined as the number of patients in which the effect of delay on survival had actually been studied. Measurement of the effects of time intervals (Criterion 10) was defined as the method used to measure delay, including means, medians, or cut-off points established *a priori* or *a posteriori* (e.g. <1 month, 1–3 months, 3–6 months, and >6 months). Studies were classified as a function of the first cut-off point used (e.g. <1 month). Multivariate analysis was a Cox's regression in all cases, except for one in which it was mentioned that 'an analysis of multiple variables' had been used. Variables included cancer stage (Criterion 13), degree of differentiation (Criterion 14), intestinal obstructions (Criterion 15) and the absence of specific symptoms (Criterion 16), and it was indicated whether each had been adjusted for by a stratified or multivariate analysis in studying the relationship between delay and survival. Each study was indexed and subsequently included in a summary chart in a spreadsheet. The articles were read and evaluated independently by two researchers. For those cases in which there were discordances between the two evaluations, both researchers reviewed the cases together until a consensus was reached.

In a second phase, it was decided to exclude the following studies: a) those with excessively restricted samples, defined as those that excluded patients who first appeared with intestinal obstruction, with tumours in stage C or D at the time of diagnosis, and who died between 1 and 3 months after surgery (surgical mortality); b) those that studied only a portion of the delay, i.e. the delay caused by the patient or the delay caused by the medical system, but not both; and c) those in