available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Lack of association between diagnostic and therapeutic delay and stage of colorectal cancer

Maria Ramos[a,*], *Magdalena Esteva*[b], *Elena Cabeza*[a], *Joan Llobera*[b], *Amador Ruiz*[c]

[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*

ARTICLE INFO

Article history:
Received 19 September 2007
Received in revised form
4 January 2008
Accepted 7 January 2008
Available online 12 February 2008

Keywords:
Colorectal neoplasms
Colonic neoplasms
Rectal neoplasms
Meta-analysis
Early diagnosis
Diagnostic techniques and procedures
Prognosis
Survival
Epidemiology

ABSTRACT

Background: A recent review suggests that there is no association between diagnostic and therapeutic delays and survival in colorectal cancer patients. However, the effect of tumour stage on the relationship between delay and survival in CRC should be clarified. We review here the evidence on the relationship between diagnostic and therapeutic delays and stage in colorectal cancer.

Methods: We conducted a systematic review of Medline, Embase, Cancerlit and the Cochrane Database of Systematic Reviews to identify publications published between 1965 and 2006 dealing with delay, stage and colorectal cancer. A meta-analysis was performed based on the estimation of the odds ratios (OR) and on a random effects model.

Results: We identified 50 studies, representing 18,649 patients. Thirty studies were excluded due to excessively restricted samples (e.g. exclusion of patients with intestinal obstruction or who died 1–3 months after surgery) or because they studied only a portion of the delay. Of the 37 remaining studies, great variability was noted in connection with the type of classification used for disease stage and the type of measurement used for the delay. Meta-analysis was performed based on 17 studies that included 5209 patients. The combined OR was 0.98 (95% confidence interval (CI): 0.76–1.25), suggesting a lack of association between delay and disease stage. In four studies, cancers of the colon and rectum were dealt with separately, and a meta-analysis was performed using the data for colon cancer (1001 patients) and for rectal cancer (799 patients). In both cases, the combined ORs overlapped 1.0, and showed opposite associations when studied separately: 0.86 (95% CI: 0.63–1.19) for the colon (i.e. more delay is associated with the earlier stage at diagnosis) and 1.93 (95% CI: 0.89-4.219) for the rectum (i.e. less delay is associated with the earlier stage).

Conclusions: When colorectal cancers are taken as a whole, there appears to be no association between diagnostic delay and disease stage when diagnosis is made. However, when cancers of the colon and the rectum are studied separately, there may be an opposite association. More studies about this issue are needed with larger and unrestricted samples.

* *Corresponding author:* Tel./fax: +34 971 176885.
E-mail address: mramos@dgsanita.caib.es (M. Ramos).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.01.011

1. Introduction

Colorectal cancer is an important public health problem worldwide, especially in wealthy countries. In Europe, when both sexes are taken together, it ranks the second highest amongst cancers in both incidence and mortality,[1] while in the United States it is the cancer with the fourth highest incidence and ranks second in terms of mortality.[2]

Survival amongst patients with colorectal cancer varies greatly amongst different geographic regions. In the United States, it is higher than in Europe: 69% versus 57% after 3 years,[3] a fact that could be linked to earlier diagnosis, since the percentage of cases that are diagnosed in early stages, the percentage of adenocarcinomas that are found when adenomas (polyps) are removed and the percentage of tumours that are removed are all higher in the United States.[4] Greater differences are seen amongst European countries, which may also be due to wide variability in access to diagnostic and therapeutic techniques.[5]

The stage when the tumour is diagnosed is the main prognostic factor in colorectal cancer, so that in Europe survival is 93% after 3 years for Duke stage A, between 91% and 74% for stage B, between 66% and 48% for stage C and 16% for stage D.[3]

There is an evidence that early diagnosis, before symptoms appear, reduces disease mortality and incidence.[6] On the other hand, when the patient already has symptoms, there is a controversy regarding the association between how long they have been present – that is, diagnostic or therapeutic delay – and survival. In the case of breast cancer, it has been shown that early diagnosis is linked to better survival, an effect that appears to be mediated by the stage of the disease when the diagnosis is made.[7]

In a recent systematic review[8] that was performed to assess how diagnostic and therapeutic delays affect survival, we have obtained contradictory results: in most cases, there was no association between delay and survival; in others, there was paradoxically an association between a longer delay and a greater survival, and in others still greater delay was associated with decreased survival. However, when the delay was adjusted for other variables having prognostic significance, such as disease stage, the association between delay and survival disappeared in all studies, which shows that disease stage could be acting as a confounder. At the same time, the results obtained suggested that the delay could affect survival differently in the case of cancers of the colon and rectum.

We found no review that looked at the link between delay and disease stages. This study aims to review and summarise the evidence accrued.

2. Patients and methods

A systematic review was carried out. The following bibliographic databases were consulted: Medline, Embase, Cancerlit and Cochrane Database of Systematic Reviews. The following search strategy was followed for all databases: (*colorectal neoplasm* OR *gastrointestinal neoplasm*) AND (*early diagnosis* OR *diagnostic delay* OR *patient delay* OR *provider delay*) AND (*diagnostic techniques and procedures* OR *stage* OR *survival* OR *prognosis*). Systematic reviews as well as original studies in English or Spanish on diagnostic or therapeutic delay in colorectal cancer were included; traditional reviews, editorials and opinion letters were not. A review was considered to be systematic if it at least described the methods followed in identifying and selecting articles. A secondary review was performed based on the bibliography included in each of the selected articles, which allowed us to identify other studies. We also used the 'related links' option in PubMed. Finally, we looked for unpublished doctoral dissertations through specific Spanish-language databases (TESEO, TDX) or general search engines (Google). The final period analysed extended from 1965 to 2006. We included all articles that dealt with the association between delay and disease stages, whether the delay was the main study variable or one of several factors under study. Our selection was based first on the title and secondly on the abstract. The review was carried out between November 2004 and February 2007.

The studies were read and assessed independently by two researchers in accordance with the criteria presented in Table 1, which were defined by the research team based on those proposed by other authors for reviewing non-experimental studies.[9–12] The sample size was taken to be the number of cases for which the delay and the disease stages were truly the subject of study, whenever this information was available. Otherwise, the stated sample size was recorded. The outcome measure for the interval was used to quantify the delay: means, medians or cut-off points established *a priori* or *a posteriori* (for instance, less than 1 month, 1–3 months, 3–6 months and more than 6 months). The studies were classified according to the first cut-off point used (for example, <1 month: less than 1 month and other longer intervals). Multivariate analysis was noted as having been performed whenever the latter was used to study the relationship between delay and stage. A specific form was prepared, followed by a summary table on graph paper. Discordant studies were reviewed by both reviewers and consensus results were derived.

In a second phase, we decided to exclude (a) studies having strictly exclusive inclusion criteria: those that excluded patients with intestinal obstruction or patients who died after surgery (surgical mortality) and (b) studies in which only a portion of the delay was taken into account, namely the part that was caused by the patient himself or by the health system.

2.1. Analysis

With the studies that were finally included in the study, a descriptive analysis following the model used by Huang[13] was carried out. A meta-analysis was performed that included all studies for which absolute figures were available. Given the wide variability in study design (especially in the definition and assessment of the delay) and the results obtained, we chose a random effects model. A delay was considered to have occurred whenever the time intervals between the first symptom and the diagnosis or treatment were longer than the first cut-off point under study in each case, and no delay was considered to have taken place if the intervals were shorter. The stage was classified as early or advanced in