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Review

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

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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.

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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

Table 1 – Quality criteria used in systematic review

No.	Criterion	Categories
1	Publication year	1. 1968–1990; 2. 1991–2000; 3. 2001–2006
2	Scope	1. Hospital; 2. Population based
3	Site	1.Colorectal; 2.Colon & rectum separately; 3.Colon; 4.Rectum
4	What is investigated?	1. Stage; 2.Survival; 3. Stage & survival
5	Sample	1. Operable cases; 2. Not restricted; 3. Intestinal obstructions excluded; 4. Deaths 1–3 months after surgery excluded
6	Sample size	1. <300; 2. 300 a 499; 3. 500 a 999; 4. 1000 or more
7	Information sources	0. Not mentioned; 1. Hospital clinical records (H-CR); 2. Interviews; 3. Also primary health care clinical records (PHC-CR)
8	Interval of time definition	1. From beginning of symptoms to diagnosis; 2. From beginning of symptoms to treatment; 9. Not mentioned
9	Manner of measuring the interval of time	1. Global; 2. Only a fragment (patient's delay or health system's delay)
10	Measurements of the effects of the interval of time	1. Average; 2. Median; 3. <1 months; 4. <2 months; 5. <3 months; 6. <4 months; 7. <5 months; 8. <6 months; 9. Quartiles
11	Measurements of the effects of survival	1. Only absolute numbers; 2. Only average or median comparisons; 3. Only correlations; 4. Survival taxes; 5. Survival curves comparison as well as survival taxes; 6.Hazard Ratio with Cox regression as well as taxes and curves
12	Multivariate analysis	0. No; 1. Yes
13	Influence of cancer stage	0. Not explored; 1. Yes
14	Influence of degree of differentiation	0. Not explored; 1. Yes
15	Influence of intestinal obstructions	0. Not explored; 1. Yes
16	Influence of group without specific symptoms	0. Not explored; 1. Yes
17	Start point of follow up	0. Not included; 1. Diagnostic; 2. Surgery; 3. Beginning of symptoms
18	Confidence intervals	0. No; 1. Yes
19	Period of monitoring	1. 4–5 years; 2. 10–20 years; 9. Not included
20	Subjects lost during monitoring	0. None; 1. Up to 5%; 2. 6–20%; 9. Not included
21	Characteristics of lost subjects	0. None or not included; 1. Similar to cases not missing; 2.Different to cases not missing

which the type of analysis used to assess the association between delay and survival was not recorded or could not be deduced.

Analysis. A descriptive analysis of all studies eventually included was performed,[29] and a random effects model was selected for meta-analysis, since studies were heterogeneous in design and in the results obtained. For meta-analyses, we calculated relative risks (RRs), thus necessitating the exclusion of studies in which the absolute numbers needed to calculate RRs were not available. The diagnostic or therapeutic delay was considered as exposition and 5-year survival as success. 'Delay' was defined as the time interval between the first symptom and diagnosis or treatment that exceeded the first cut-off point for each study, and 'no delay' was the interval below the first cut-off point. Dersimonian and Laird's test and a Galbraith plot were used to examine the heterogeneity of RR estimations; a combined RR was obtained and Begg test and an Egger test and in a graphic form by a 'funnel plot' and an Egger graphic. Finally, a meta-regression analysis was attempted.[30] To determine whether the results were dependent on any of the assumptions, the following sensitivity analyses were performed: 1) cancers of the colon and rectum were assessed separately; 2) a cutoff point for delay was defined; and 3) studies initially excluded were included. The program Epidat was used.[31]

3. Results

Forty-one studies were identified: Ten from Medline, two from Embase and the rest from the secondary review. No systematic review was identified, and one that did not comply with the definition was excluded.[32] The characteristics of the remaining 40 studies[5,9,18–24,33–63] are shown in Table 2. All were original articles, except for one unpublished doctoral thesis.[56] Two of the publications belonged to the same study, one published results on the colon[21] and the other on the rectum[22]; they were therefore considered separately. Similarly, three publications originated from the same hospital and stemmed from the same hospital registry of tumours, but at different time periods[24,57,50]; they, too, were considered separately. In total, the 40 studies included 20,440 individuals with colorectal cancer. In 26 publications (65%) the cancers were colorectal, in seven (17.5%) colon and rectum were considered separately, in four (10%) only colon cancers were included (two of these only right colon cancers), and in three (7.5%) only rectal cancers. Four studies also included cancers at other locations[20,24,57,50]; we included only the subsets of colon and rectal cancers, provided that the results were analysed independently of those at other locations. This last aspect obliged us in one of the studies to obtain the doctoral thesis[64] from which the article was derived.[50]

The majority of the studies were from hospitals, with only six being of persons in the general population. More than half the studies (57.5%) used restricted samples. The period of follow up was recorded in 37 of the 40 studies, and varied between 3 and 20 years. None of the studies considered the onset of symptoms as the starting point; in 23 studies, the starting point was not mentioned. In 19 studies there were no losses to follow up or it was not mentioned. Of the remaining 20 studies, 12 reported that $\leqslant$5% of patients were lost to

Table 2 – Characteristics of 39 studies of delay and survival

Year	First author	Country	Site	Sample	Size	Sources[a]	End-point of delay	Cut-off points	Survival	Start follow–up	CI	Meta-analysis
1962	Welch C[18]	United States	Colorectal	Operable cases	1195	Not included	Date of surgical intervention	Averages	Taxes	Surgery	No	No
1968	Copeland E[33]	United States	Colorectal	Not restricted	980	Not included	Date of surgical intervention	< 5 months	Taxes	Surgery	No	Yes
1970	MacLeod J[34]	Canada	Colorectal	Not restricted	370	H-CR	Date of surgical intervention	< 4 months	Curves	Surgery	No	No
1977	Irvin T[19]	UK	Colorectal	Operable cases	321	H-CR	Date of diagnosis	< 5 months	Taxes	Not included	No	Yes
1981	Polissar L[35]	United States	Colorectal	Operable cases	154	Interview	Date of diagnosis	< 6 months	HR/Cox	Diagnosis	Yes	Yes
1982	Pescatori M[23]	Italy	Colorectal	Operable cases	161	H-CR	Date of diagnosis	< 3 months	Taxes	Not included	No	Yes
1982	Jolly K[36]	New Zealand	Colorectal	Not restricted	455	H-CR	Date of surgical intervention	< 2 months	Taxes	Surgery	No	No
1984	Schillaci A[37]	Italy	Colorectal	Not restricted	162	Not included	Date of surgical intervention	<3 months	Curves	Not included	No	No
1985	Khubchandani M[38]	United States	Colorectal	Not restricted	194	H-CR	Date of surgical intervention	< 3 months	Curves	Not included	No	No
1985	Chapuis P[39]	Australia	Colorectal	Operable cases	709	Not included	Not included	< 1 month	HR/Cox	Surgery	No	No
1987	Goh HS[40]	India	Colorectal	Not restricted	219	Not included	Date of diagnosis	<3 months	Curves	Not included	No	No
1988	Wiggers T[41]	Netherlands	Colorectal	Deaths after surgery excluded	310	Interview	Not included	< 2 months	HR/Cox	Not included	No	No
1989	Elorza J[42]	Spain	Colorectal	Operable cases	131	HC-CR	Date of surgical intervention	< 1 months	Curves	Surgery	No	No
1989	García D[43]	Spain	Colorectal	Operable cases	307	H-CR	Date of surgical intervention	< 3 months	Medians	Diagnosis	No	No
1989	Barillari P[5]	Italy	Colorectal	Obstructions excluded	571	Not included	Date of surgical intervention	< 3 months	Curves	Not included	No	No
1989	Hughier M[44]	France	Colorectal	Stages C & D excluded	252	Not included	Date of surgical intervention	<3 months	HR/Cox	Not included	No	No
1991	Crucitti F[45]	Italy	Colorectal	Operable cases	361	Not included	Date of surgical intervention	<3 months	Curves	Not included	No	No
1992	Ponz de Leon M[46]	Italy	Colorectal	Not restricted	98	Interview	Date of diagnosis	< 2 months	Curves	Diagnosis	No	Yes
1994	Deans G[47]	Ireland	Colorectal	Deaths after surgery excluded	312	H-CR	Not included	< 3 months	HR/Cox	Not included	No	No
1997	Mulcahy H[9]	Ireland	Colorectal	Not restricted	777	Interview	Date of surgical intervention	< 1 month	HR/Cox	Not included	Yes	Yes

1999	Roncoroni L[48]	Italy	Colorectal	Operable cases	100	Interview	Date of surgical intervention	< 3 months	HR/Cox	Surgery	No	No
1999	Park Y[49]	Korea	Colorectal	Deaths after surgery excluded	2230	H-CR	Not included	< 5 months	Taxes	Not included	No	No
2002	Fernández E[50]	Spain	Colorectal	Not restricted	150	Interview	Date of diagnosis	< 2 months	HR/Cox	Diagnosis	Yes	No
2004	González F[51]	Spain	Colorectal	Obstructions excluded	660	H-CR	Date of surgical intervention	< 3 months	Curves	Not included	Yes	No
2005	Bharucha S[52]	UK	Colorectal	Obstructions excluded	582	H-CR	Date of surgical intervention	Quartiles	Curves	Not included	No	No
2006	Stapley S[53]	UK	Colorectal	Not restricted	349	PHC-CR	Date of diagnosis	Quartiles	HR/Cox	Not included	No	No
1974	Lim B[20]	United States	Colon & rectum	Not restricted	217	H-CR	Only a portion of delay	Averages	Correlation's	Diagnosis	No	No
1985	Hillon P[54]	France	Colon & rectum	Not restricted	894	H-CR	Date of diagnosis	< 6 months	Taxes	Not included	No	No
1988	Bako G[55]	Canada	Colon & rectum	Not restricted	265	Not included	Date of diagnosis	< 1 month	HR/Cox	Not included	No	No
1990	Rifà J[56]	Spain	Colon & rectum	Not restricted	895	H-CR	Date of diagnosis	< 5 months	Taxes	Not included	Yes	No
1991	Porta M[24]	Spain	Colon & rectum	Not restricted	328	H-CR	Date of diagnosis	< 3 months	Medians	Not included	No	No
1994	Maguire A[57]	Spain	Colon & rectum	Not restricted	441	H-CR	Date of diagnosis	< 1 month	HR/Cox	Diagnosis	Yes	No
2004	Olsson L[58]	Sweden	Colon & rectum	Obstructions excluded	210	Interview	Date of surgical intervention	< 5 months	Curves	Not included	Yes	No
1981	McDermott F[21]	Australia	Colon	Deaths after surgery excluded	711	Not included	Date of surgical intervention	< 3 months	Curves	Surgery	No	No
1989	Fegiz G[59]	Italy	Colon	Obstructions excluded	195	Not included	Date of surgical intervention	< 3 months	Curves	Not included	No	No
1992	Auvinen A[60]	Finland	Colon	Not restricted	2969	H-CR	Date of diagnosis	< 1 month	HR/Cox	Not included	Yes	No
1993	Goodman D[61]	UK	Colon	Obstructions excluded	136	H-CR	Date of surgical intervention	< 4 months	Curves	Surgery	No	No
1973	Devlin H[62]	UK	Rectum	Operable cases	286	H-CR	Date of surgical intervention	< 1 month	Not included	Not included	No	No
1981	McDermott F[22]	Australia	Rectum	Deaths after surgery excluded	1081	Not included	Date of surgical intervention	< 3 months	Curves	Surgery	No	No
1988	Stahle E[63]	Sweden	Rectum	Operable cases	316	H-CR	Date of surgical intervention	< 1 month	Curves	Surgery	Yes	Yes

a H-CR: Hospital clinical records; PHC-CR: Primary Health Care clinical records.

follow up, and only one reported that loss to follow up exceeded 20%.[42]

Fourteen studies (35.9%) were discarded (Fig. 1), thus leaving 26, which included 13,301 persons with colorectal cancer. Table 3 summarises their characteristics. Twelve studies took into account tumour stage in analysing the effect of delay on survival, but few studies considered other factors that could have affected survival, such as the degree of tumour differentiation (only four studies), the presence of intestinal obstruction (four studies) and subgroups of patients without specific symptoms (two studies).

Of the 26 studies included, 20 found no association between diagnostic or therapeutic delay and survival rate,[9,19,24,35–40,42,43,45,46,48,50,53,55,57,60,63] four studies found that longer delay was related to a higher rate of survival[23,33,54,56] and two found that longer delay was associated with a poorer rate of survival.[18,34] As shown in Table 3, the studies in which no association was found had different sample sizes. Longer delay tended to be related to longer survival in nine studies[9,23,24,33,36,42,54,56,60] (in three, this applied only to colon cancers[24,54,60]) and to poorer survival in eight studies[18,19,34,43,48,54,57,63] (in two, this applied only to rectal cancers[54,57]); in the remaining ten studies, there was no association.[35,37,38,40,45,46,50,53,55,63]

When cancers of the colon and rectum were considered separately, we observed an association between longer delay and increased survival only for colon tumors.[54,56] There was also no association between delay and survival in any of the studies in which multivariate analyses were performed or in those that took into account the effect of tumour stage, de-

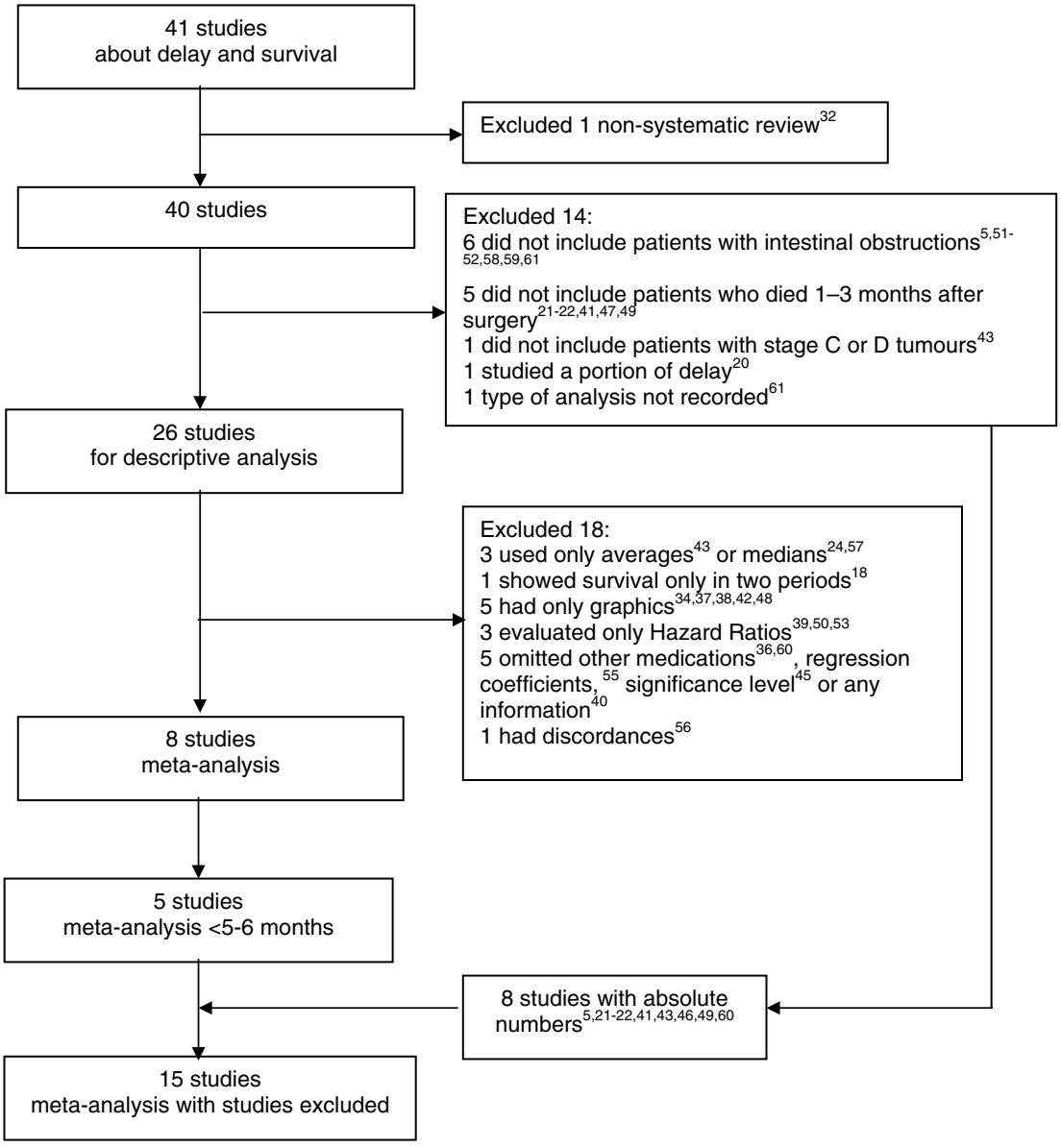

Fig. 1 – Summary of exclusion of studies.

Table 3 – Characteristics of studies after exclusion of those with excessively restricted samples, those that studied only a portion of delay and those in which type of analysis was not recorded

Criterion	Categories	Number of studies	Sample size	Results		
				>delay >survival	<delay >survival	No association
Continent	Europe	17	8.760	3	0	14
	America	6	3.158	1	2	3
	Asia	1	219	0	0	1
	Australia	2	1.164	0	0	2
Site	Colorectal	19	7.193	2	2	15
	Colon & rectum	5	2.823	2	0	3
	Colon	1	2.969	0	0	1
	Rectum	1	316	0	0	1
Year	From 1968 to 1990	17	7.728	4	2	11
	From 1991 to 2000	8	5.224	0	0	8
	From 2001 to 2006	1	349	0	0	1
Scope	Hospital	20	7.942	2	2	16
	Population based	6	5.359	2	0	4
Sample characteristics	Not restricted	15	9.176	3	0	12
	Operable cases	11	4.125	1	2	8
Sample size	< 300	10	1.634	1	0	9
	300–499	9	3.248	0	1	8
	500–999	5	4.255	3	0	2
	⩾1000	2	4.164	0	1	1
Information sources	Hospital clinical records	13	7.782	3	1	9
	Interviews	5	1.279	0	0	5
	PHC clinical records	1	349	0	0	1
	Not included	7	3.891	1	1	5
Interval	From beginning of symptoms to diagnosis	13	7.244	3	0	10
definition	From beginning of symptoms to surgery	12	5.348	1	2	9
	Not included	1	709	0	0	1
Measurement of the	Averages	2	1.502	0	1	1
effects of the time interval	<1 month and other portions	6	2.639	0	0	6
	<2 months and other portions	3	703	0	0	3
	<3 months and other portions	8	4.494	1	0	7
	<4 months and other portions	1	370	0	1	0
	<5 months and other portions	3	2.196	2	0	1
	<6 months and other portions	2	1.048	1	0	1
	Quartiles	1	349	0	0	1
Measurement of the	5 year's taxes of survival	7	4.901	4	1	2
effects of survival	Curves	8	1.851	0	1	7
	Hazard Ratio/ Cox regression	9	5.914	0	0	9
	Averages/Medians	2	635	0	0	2
Multivariate analysis	Yes	12	6.770	0	0	12
	No	14	6.531	4	2	8
Confidence intervals	Yes	6	5.548	1	0	5
	No	20	7.743	3	2	15
Influence of the	Yes	12	4.114	0	0	12
cancer stage	No	14	9.187	4	2	8
Influence of degree of	Yes	4	1.275	0	0	4
differentiation	No	22	12.026	4	2	16
Influence of intestinal	Yes	4	1.474	0	0	4
obstruction	No	22	11.827	4	2	16
Influence of group without	Yes	2	344	0	0	2
specific symptoms	No	24	12.957	4	2	18
TOTAL		26	13.301	4	2	20

gree of differentiation, intestinal obstructions or the absence of specific symptoms.

To perform a meta-analysis, it was necessary to exclude 18 additional studies (Fig. 1), either because they lacked the absolute numbers necessary for calculating RRs or because the data were discordant when the cancers of the colon and of the rectum were considered separately and together. Of those 18, 15 did not find an association between delay and

survival, one found an association between longer delay and longer survival and two found an association between longer delay and poorer survival. The remaining eight studies, representing a population of 3680 persons, were suitable for meta-analysis. According to Dersimonian and Laird's test, there was no heterogeneity ($p = 0.3395$). The Galbraith plot (Fig. 2) shows that seven of these eight studies were within the range bounded by the upper and lower limits, statistically corroborating the lack of heterogeneity. According to the random effects model, the combined RR was 0.92 (confidence interval (CI) 95%: 0.87–0.97), which supports the hypothesis that longer delay is related to better survival. The forest plot (Fig. 3) showed that this result was obtained in most of the studies included. The results of Begg ($p = 0.9015$) and Egger ($p = 0.6602$) tests were not significant, suggesting the absence of publication bias.

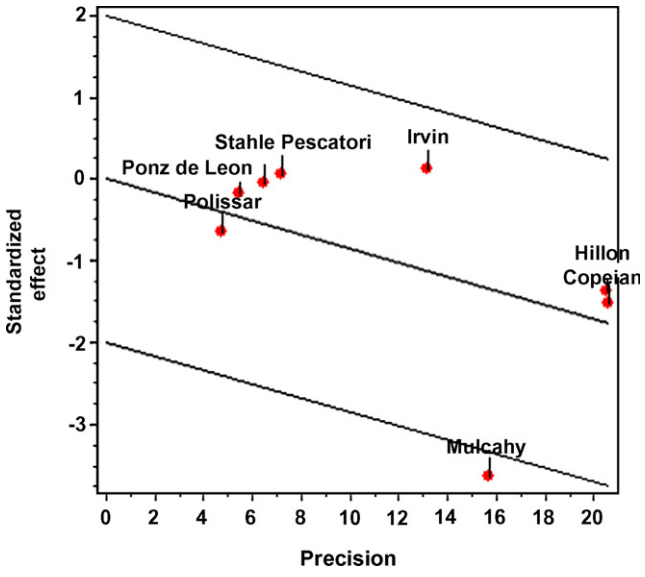

Fig. 2 – Galbraith graphic.

Analysis of sensitivity. 1) It was not possible to perform a meta-analysis separately for the colon and the rectum, since, of the eight included studies, six studied tumours of the colon and rectum together, one studied colon and rectal cancers separately, and one studied only rectal tumours. 2) The meta-analysis was repeated with 'delay' defined as an interval between first symptoms and diagnosis or treatment longer than 5–6 months, this being the cut-off point that allowed the inclusion of more studies. Nevertheless, we had to omit two of these eight studies because they used incompatible intervals, one using <2 months and >2 months, and the other <1 month, 2–8 months and >8 months. The six remaining studies, which evaluated 3277 patients, yielded a combined RR according to the random effects model of 0.92 (CI 95%: 0.87–0.98). 3) The meta-analysis was repeated, while including eight of the 14 excluded papers with available absolute numbers. This meta-analysis included 16 studies, with a population of 8533 patients. According to the random effects model, the combined RR was 0.93 (CI 95%: 0.86–0.99).

Finally, we assessed the possibility of performing a meta-regression using data from the eight studies initially included in the meta-analysis. Among the variables considered were tumour location (colon or rectum), stage, degree of differentiation, intestinal obstructions and the presence of non-specific symptoms. Meta-regression was rejected since only one study analysed the colon and rectum separately, only three took tumour stage into account, only one each considered the degree of differentiation and intestinal obstructions and none separated out the subgroup of patients without specific symptoms.

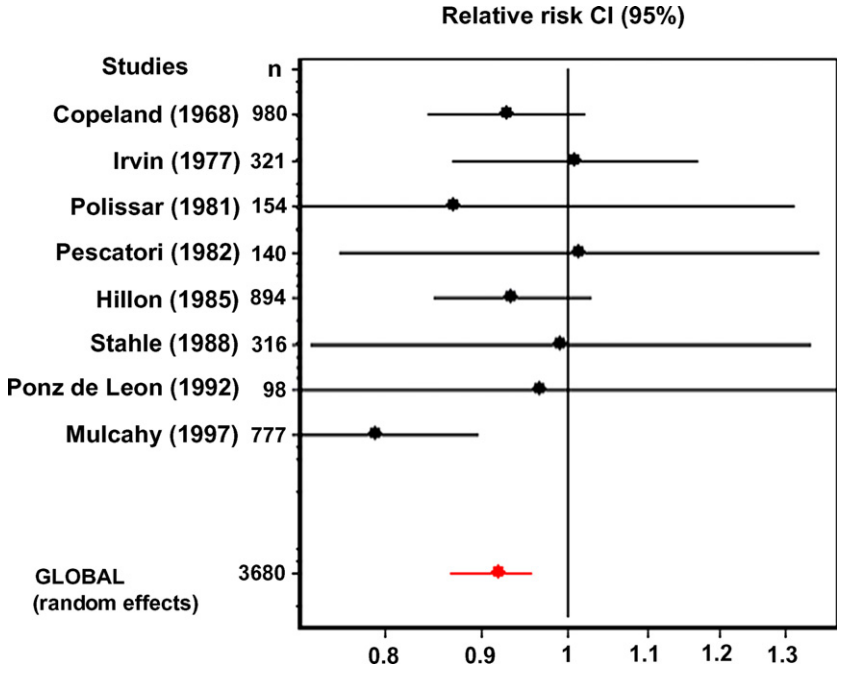

Fig. 3 – Forest plot.

4. Discussion

The systematic review did not produce an unequivocal answer to the question of whether diagnostic or therapeutic delay influences survival in CRC. Our review, however, enabled us to identify deficiencies in the studies reviewed, and to put forward several hypotheses. Although the results of the meta-analysis suggest that longer delay in CRC is related to improved survival, this is by no means certain.

Limitations of the systematic review. The term 'delay' is not a descriptor, nor is it present in the title or abstract of many studies, since it is not the principal variable but just one of the factors studied. In addition, we experienced difficulties in identifying relevant unpublished studies, principally doctoral theses, suggesting that it may be beneficial to have an international directory of theses. For all these reasons, this first review using descriptors and keywords had a very low sensitivity. Finally, we could not rule out the possibility that we missed other relevant studies.

Limitations of the studies. The majority of the studies investigated patients with colorectal cancer, although some also included other cancers of the digestive tract or other locations. Epidemiological,[50,65] etiological[66,67] and genetic[68] factors all suggest that colorectal cancer is not a single entity and that the colon and rectum should be evaluated separately, thus revealing associations that may otherwise remain hidden. Thus, for example, although there was no association between alcohol consumption and colorectal cancer, separate evaluation showed that alcohol was associated with tumours of the distal colon and rectum.[69] The apparently beneficial effect of diagnosis or treatment delay has been observed with greater frequency in colon cancer,[21,24,54,56] whereas the contrary effect has been observed in rectal cancer.[22,65,71] Despite the difficulty in classifying recto-sigmoid neoplasias as being of the colon or of the rectum,[70] our findings suggest that future studies of delay and survival in CRC should evaluate tumours of the colon and rectum separately.

Unfortunately, more than half the studies used restricted samples, which introduces selection bias. We opted to include only studies restricted to operable patients, since these included patients at all colorectal tumour stages. However, we excluded those studies that excluded patients who were admitted to casualty departments with all the signs of intestinal obstruction, as well as those who died 1 to 3 months after surgery. The authors of one study attribute their results to this factor.[48] In our repetition of the meta-analysis, however, inclusion of these excluded studies did not alter the results.

Another problem with the studies assessed is that the majority measure survival starting from diagnosis or from surgery rather than symptom onset. Beginning at the earlier time point would avoid lead-time bias, in which an apparent increase in survival could be attributed solely to an earlier diagnosis.[15,72] We are conscious, however, of the difficulty involved in determining the exact moment of symptom onset.

There was great variability among studies, both in the definition of delay and in the manner of measuring it, which has not yet been resolved.[73] The consequences of this variability are reflected in the present meta-analysis, in that we were able to include only about one third of the patients in the studies that were not excluded (31%) or one-fifth of the total number of patients (18%). Differences were observed in defining the endpoint of the 'delay period'; in some studies, it was the date of diagnosis and in others the date of surgical intervention. In measuring the 'delay', many studies used different cut-off points, which were usually established *a priori* and in an arbitrary manner. The median values were used to establish the cut-off points in only two studies,[25,57] although median is more appropriate than mean for determining the delay, since the distribution curves of the median values are deflected to the right,[71] and the mean underestimates this. All these aspects should be taken into account in design studies comparing delay and survival, especially the inclusion of absolute numbers in the papers.

We have observed disparate and contradictory results. The majority of the studies did not find an association between delay and survival or they observed that longer delay was associated with longer survival, a finding that is counter-intuitive. Studies that considered the effects of other variables with known or suspected prognostic value did not find an association between delay and survival. In contrast, the meta-analysis showed a weak degree of association (RR = 0.9) between delay and survival, but, unfortunately, a meta-regression could not be performed. In addition to tumour location, variables such as tumour stage, degree of differentiation, intestinal obstruction and the absence of specific symptoms may act as confounding factors and should therefore be included in the analysis of future studies.

Tumour stage at time of diagnosis or of surgery may be an intermediate factor in the chain of causality between delay and survival.[74] In breast cancer, at least, the effect of delay on survival is thought to be due principally to tumour stage.[15] However, it may also be a confounding factor. Although some studies suggested that stage is associated with delay,[75–78] others did not.[19,23,38,48] At the same time, tumour stage is the main prognostic factor in CRC, making it important to review in depth the effect of stage on survival.

Although some studies found an association between the degree of tumour differentiation and delay,[4,21,62,79] other studies found no association.[5,48,80] Additionally, degree of differentiation has been found to be an independent prognostic factor in CRC,[39,50,63,81–83] but not all studies support these findings.[79,84–86] With regard to chain of causality, we suggest that the degree of differentiation can be a 'proxy' variable for tumour aggressiveness.[85]

Patients with intestinal obstruction are a subgroup of CRC patients that show short delay in diagnosis,[19,79,87] but have a poorer prognosis than patients undergoing elective surgery.[11,50] Intestinal obstruction, however, is a prognostic factor only in colon cancer patients.[88] In contrast, we found no studies that explored the association between delay and the presence of non-specific symptoms (anaemia, asthenia, etc.), although there is evidence that patients with non-specific symptoms as well as those without symptoms have a better prognosis.[5,38,59,61]

Finally, other factors possibly related to cancer survival should be considered, including factors reflecting the interaction between the tumour and the host, such as the functional state of the patient and the degree of comorbidity[89]; molecular markers, whose prognostic effect is under investigation but has not yet been confirmed for CRC[90,91]; and factors re-

lated to the quality of the healthcare system (accessibility, diagnostic policy or waiting lists), which influence delay.[6,7,61,76,81] In addition, the differences among European countries in CRC patient survival should be assessed.[2]

The absence of association between delay and survival in CRC strengthens the importance of CRC diagnosis prior to symptom appearance. Screening has been found to reduce the mortality as well as the incidence of CRC.[92] Even if a reduction in delay does not result in enhanced survival, the evaluation of the programme 'Two Weeks', run by the National Health Service[93] for the rapid diagnosis of cancer, observed that for CRC, a reduction in delay minimises complications such as intestinal obstructions, suggesting it may have a beneficial effect on survival.

In summary:

1. The results of this review suggest that there is no association between diagnostic and therapeutic delay and survival in colorectal cancer patients.
2. It is appropriate to study the colon and rectum separately.
3. The effect of tumour stage on the relationship between delay and survival in CRC should be clarified, as well as its association with delay.
4. In order to study the relationship between delay and survival, it is necessary to adjust for other factors that may confound the results.

Conflict of interest statement

None declared.

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