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Review

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

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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.

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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

Table 1 – Criteria used to assess articles

Criterion	Categories
Year of publication	1. 1968–1990; 2. 1991–2000; 3. 2001–2006
Study setting	1. Hospital-based; 2. Population-based
Tumour site	1. Colorectal; 2. Colon and rectum separately; 3. Colon; 4. Rectum
Study variable	1. Stage; 2. Survival; 3. Stage and survival
Sample	1. Amenable to surgery; 2. Not restricted; 3. Obstructions excluded; 4. Those dying 1–3 months after surgery excluded
Sample size	1. <300; 2. 300–499; 3. 500–999; 4. 1000 or more
Information sources	0. Not given; 1. Hospital clinical history; 2. Interview; 3. Have also used primary care clinical histories
Definition of delay	1. From the onset of symptoms to diagnosis; 2. From the onset of symptoms to treatment 9. Unclear
Measures of the time interval	1. Overall; 2. Only a portion (delay due to patient, delay due to health system)
Stage classifications	1. Dukes' original (ABC); 2. Dukes' modified (ABCD and others); 3. Dukes' simplified (A + B/C + D); 4. TNM; 5. ACPS (Australia); 6. UICC (Union Internationale Contre le Cancer [International Union Against Cancer]); 7. Localised/Regional/Disseminated
Measures of the delay	1. Means; 2. Medians; 3. <1 month; 4. <2 months; 5. <3 months; 6. <4 months; 7. <5 months; 8. <6 months; 9. Quartiles
Measurements of the delay by disease stage	1. Comparison of means or medians; 2. Frequencies; 3. Absolute figures; 4. Correlations; 5. Graphics; 9. Not given
Multivariate analysis	0. No; 1. For studying delay and survival; 2. For studying delay and disease stages
Confidence intervals (CI)	0. No; 1. Yes

accordance with the following criteria: Dukes stages A and B (or their equivalents in other classification schemes) were defined as early stage, whereas Dukes stages C and D (or their equivalents) were defined as advanced stage. For calculating the odds ratios (OR), the delay was treated as the exposure variable, and the disease stage at the time of diagnosis or treatment was treated as the outcome variable. Dersimonian's and Laird's tests were used, along with Galbraith's graph, to assess the presence of heterogeneity amongst the studies analysed; ORs were calculated for the individual studies as well as for all studies combined, and a 'forest plot' was used to represent this. Publication bias was assessed by means of Begs' and Egger's tests and represented on a 'funnel plot' and Egger's graph. The following sensitivity analyses were performed: (1) colon and rectum for studies that gave this information separately; (2) using a different definition of early and advanced stages, so that only Duke's stage A (or its equivalent) was considered to be early stage, and the rest (B, C and D) were considered to be advanced stages; (3) for those studies in which means were used to represent the delay, by comparing the means for extreme stages: A and D; and (4) by reincorporating studies that were excluded initially because of lack of sufficient information. Epidat was the package used to analyse the data.[14]

3. Results

In all, 50 studies (12 in Medline, 4 more in Embase and the rest through secondary searches) were found,[15–64] for a total of 18,649 individuals with cancer of the colon or rectum. Their characteristics are shown in Table 2. One of the studies is a systematic review of the effect of a rapid diagnostic programme (2 weeks) on disease stage in colorectal cancer.[42] In 31 of the 50 papers, both colon cancer and rectal cancer were studied together; in 10, both diseases were studied separately, 5 included only cancers of the colon, and 4 included only cancers of the rectum. Four studies also included cancers in other sites.[25,33,49,50] In these latter studies, we only took into account the sub-samples comprised of cancers of the colon and rectum, and only when these were studied separately from cancers in other sites. Most studies were hospital-based, and only five were population-based. One in three studies was carried out in the United Kingdom. In 42% of the studies, the influence of the delay on survival was examined, in addition to disease stage.

Thirty studies were eliminated (Fig. 1). Thus, 37 remained, for a total of 11,999 individuals with colorectal cancer. Table 3 summarises the main features of these studies. We see that most samples are small and that various ways of measuring the delay and of classifying the stage were used. Multivariate analyses to assess the influence exerted by the delay on disease stage were performed in only two studies that also included age, sex, and, in one case, tumour site. In another six studies, multivariate analysis was performed to study the influence of delay on survival, with disease stage being one of the variables included.

In 26 of the 37 studies, no statistically significant association was noted between delay and disease stages;[15–18,20,21,23,27,30,32,34,36–39,44,45,47,49,50,52,54,57,59,61,64] in 4, a longer delay was associated with less advanced disease[19,25,29,35,51] (in one case in the colon only[51]), and in 7, a shorter delay was associated with less advanced disease[24,26,28,51,53,55,63] (in one case in the rectum only[51]). Independently of statistical significance, in 5 studies a greater delay was associated with disease at an earlier stage;[19,25,29,30,35] in 12, a shorter delay was associated with disease at an earlier stage,[17,20,24,26,28,32,36,38,44,45,53,63] and no association was noted in the remaining studies.

Table 3 shows the results obtained in the different studies in light of each study's main features. We can see that most of the studies found no association between delay and disease stages independently of sample characteristics (unrestricted

Table 2 – Description of each of the studies of delay and stage

Year	1st author	Country	Site	Sample	Size	Sources[a]	Definition of delay	Measure of delay[b]	Stage classification[c]	Measure of disease stage	Multivariate analysis	Meta-analysis
1970	McLeod[15]	Canada	Colorectal	Amenable to surgery	370	H CH	Until treatment	<2 months and >	Dukes modif.	Frequencies	No	Yes (OR)
1970	Clarke[16]	New Zealand	Colorectal	Amenable to surgery	208	H CH	Until treatment	<1 months and >	Dukes simpl.	Graphics	No	No
1977	Irvin[17]	United Kingdom	Colorectal	Amenable to surgery	321	H CH	Until diagnosis	<5 months and >	Dukes orig.	Frequencies	Superv	Yes (OR)
1979	Holliday[18]	United Kingdom	Colorectal	Amenable to surgery	193	Interview	Until treatment	Means	Dukes orig.	Means	No	No
1979	Basset[19]	Australia	Colorectal	Not restricted	230	H CH	Until diagnosis	Means	Dukes modif.	Means	No	No
1980	Rubin[20]	Israel	Colorectal	Amenable to surgery	100	Interview	Until treatment	Means	Dukes orig.	Means	No	Yes (means)
1982	Pescatori[21]	Italy	Colorectal	Amenable to surgery	140	H CH	Until diagnosis	<3 months and >	Dukes modif.	Frequencies	No	Yes (OR)
1982	Nilsson[22]	Sweden	Colorectal	Not restricted	284	H CH	Only a portion	<6 months and >	Dukes orig.	Absolute figures	No	No
1982	Jolly[23]	New Zealand	Colorectal	Not restricted	455	H CH	Until treatment	<2 months and >	Dukes simpl.	Graphics	No	No
1982	Devesa[24]	Spain	Colorectal	Not restricted	78	Not given	Until diagnosis	Means	LRD	Means	No	Si (means)
1983	Bosch[25]	Spain	Colorectal	Not restricted	173	H CH	Until diagnosis	Means	LRD	Means	No	Yes (means)
1984	McArthur[26]	United Kingdom	Colorectal	Not restricted	97	PC CH	Until treatment	<2 months and >	LRD	Frequencies	No	Yes (OR)
1985	Khubchandani[27]	USA	Colorectal	Not restricted	192	H CH	Until treatment	<3 months and >	Dukes modif.	Frequencies	No	Yes (OR)
1986	Robinson[28]	Israel	Colorectal	Not restricted	424	Not given	Until diagnosis	<1.5 months and >	Dukes simpl.	Frequencies	No	Yes (OR)
1986	Stubbs[29]	United Kingdom	Colorectal	Amenable to surgery	207	Not given	Until diagnosis	<3 months and >	Dukes modif.	Absolute figures	No	Yes (OR)
1989	García[30]	Spain	Colorectal	Amenable to surgery	307	CH	Until treatment	Means	Dukes modif.	Means	No	Yes (means)
1989	Barillari[31]	Italy	Colorectal	No obstructions	571	Not given	Until treatment	<3 months and >	TNM	Frequencies	No	No
1989	Ratcliffe[32]	United Kingdom	Colorectal	Amenable to surgery	280	Interview	Until treatment	Medians	Dukes orig.	Medians	No	No
1990	Mor[33]	USA	Colorectal	Not restricted	244	Interview	Only a portion	<3 months and >	LD	Frequencies	Yes	No
1991	Kyle[34]	Saudi Arabia	Colorectal	Amenable to surgery	155	H CH	Until treatment	<3 months and >	ACPS	Correlations	No	Yes (OR)
1997	Mulcahy[35]	Ireland	Colorectal	Not restricted	777	Interview	Until treatment	<1 months and >	TNM	Frequencies	Superv	Yes (OR)
1999	Roncoroni L.[36]	Italy	Colorectal	Amenable to surgery	100	Interview	Until treatment	<3 months and >	Dukes modif.	Frequencies	Superv	Yes (OR)
1999	Majumdar[37]	USA	Colorectal	Not restricted	168	PC CH	Until diagnosis	Medians	Dukes modif.	Graphics	No	No
2000	Young[38]	Australia	Colorectal	Amenable to surgery	100	Interview	Until diagnosis	<3 months and >	ACPS	Frequencies	Yes	Yes (OR)
2002	Kiran[39]	United Kingdom	Colorectal	Amenable to surgery	220	H CH	Until treatment	<6 months and >	Dukes modif.	Graphics	No	No
2004	Gonzalez[40]	Spain	Colorectal	No obstructions	660	H CH	Until treatment	<3 months and >	TNM	Frequencies	No	No
2005	Bharucha[41]	United Kingdom	Colorectal	No obstructions	542	H CH	Until treatment	Quartiles	Dukes orig.	Frequencies	No	No
2006	Thorne[42]	United Kingdom	Colorectal	RS[d]	2440	SR	Only a portion	<15 d and >	SR	SR	SR	No
2006	Khattak[43]	United Kingdom	Colorectal	Amenable to surgery	101	Interview	Only a portion	Medians	Dukes modif.	Medians	No	No
2006	Gómez[44]	Spain	Colorectal	Amenable to surgery	99	Interview	Until diagnosis	Means	Dukes modif.	Means	No	Si (medias)
2006	Stapley[45]	United Kingdom	Colorectal	Not restricted	349	PC CH	Until diagnosis	Quartiles	Dukes modif.	Frequencies	No	Si (OR)
1965	Rowe-Jones[46]	United Kingdom	Colon and rectum	Amenable to surgery	200	Interview	Only a portion	<2 months and >	Dukes orig.	Absolute figures	No	No
1968	Keddie[47]	United Kingdom	Colon and rectum	Not restricted	254	Not given	Until diagnosis	<1 months and >	Dukes modif.	Correlations	No	Si (OR)
1986	Graffner[48]	Sweden	Colon and rectum	Amenable to surgery	100	Interview	Only a portion	<3 months and >	Dukes modif.	Absolute figures	No	No
1991	Porta[49]	Spain	Colon and rectum	Not restricted	328	H CH	Until diagnosis	<3 months and >	LRD	Means	No	No
1994	Maguire[50]	Spain	Colon and rectum	Not restricted	441	H CH	Until diagnosis	<1 months and >	LRD	Medians	Superv	No
1996	Arbman[51]	Sweden	Colon and rectum	Amenable to surgery	546	Not given	Until diagnosis	<1 months and >	Dukes modif.	Frequencies	Yes	Si (OR)
1999	Wheeler[52]	United Kingdom	Colon and rectum	Amenable to surgery	200	Interview	Until treatment	Means	Dukes orig.	Means	No	No
2003	Langenbach[53]	Germany	Colon and rectum	Not restricted	70	Interview	Until treatment	Medians	UICC	Correlations	No	No
2004	Olsson[54]	Sweden	Colon and rectum	Not restricted	164	Interview	Until treatment	<6 months and >	Dukes modif.	Absolute figures	No	Yes (OR)
2006	Korsgaard[55]	Denmark	Colon and rectum	Not restricted	733	Interview	Until treatment	<2 months and >	Dukes modif.	Frequencies	No	Yes (OR)
1981	McDermott[56]	Australia	Colon	3-month survivors	601	Not given	Until treatment	<3 months and >	Dukes modif.	Frequencies	No	No
1986	Mate[57]	Spain	Colon	Amenable to surgery	42	H CH	Until diagnosis	Means	Dukes modif.	Means	No	Yes (means)
1989	Fegiz[58]	Italy	Right colon	No obstructions	195	Not given	Until treatment	<3 months and >	Dukes modif.	Absolute figures	No	No
1992	Auvinen[59]	Finland	Colon	Not restricted	2969	H CH	Until diagnosis	<3 months and >	TNM	Frequencies	Superv	No
1993	Goodman[60]	United Kingdom	Right colon	No obstructions	136	H CH	Until treatment	<3 months and >	Dukes orig.	Frequencies	No	No
1973	Devlin[61]	United Kingdom	Rectum	Not restricted	286	HCH	Until treatment	<1 months and >	Dukes orig.	Not given	No	No
1981	McDermot[62]	Australia	Rectum	3-month survivors	1076	Not given	Until treatment	<3 months and >	Dukes modif.	Frequencies	No	No
1985	Pahlman[63]	Sweden	Rectum	Amenable to surgery	135	Not given	Until diagnosis	<3 months and >	Dukes modif.	Frequencies	No	Yes (OR)
2005	Ristvedt[64]	USA	Rectum	Not restricted	87	Interview	Until diagnosis	<1 months and >	TNM	Frequencies	No	Yes (OR)

a H CH: hospital clinical history; PC HC: also the primary care clinical history.

b If means, medians or cut-off points are used (for example, <1 month and >: <1 month and other longer time intervals).

c Dukes' original: A, B and C; Dukes' modified: modifications to the original classification: A, B, C and D, Astller and Coller or others; Dukes simplified: simplifications to Dukes: A + B/C + D; LRD: localised, regional and disseminated; LD: localised and non-localised; TNM: tumour size, lymph nodes and metastases; ACP: Australian Clinicopathological Stade; UICC: Union Internationale Contre le Cancer [International Union Against Cancer].

d SR: Systematic review.

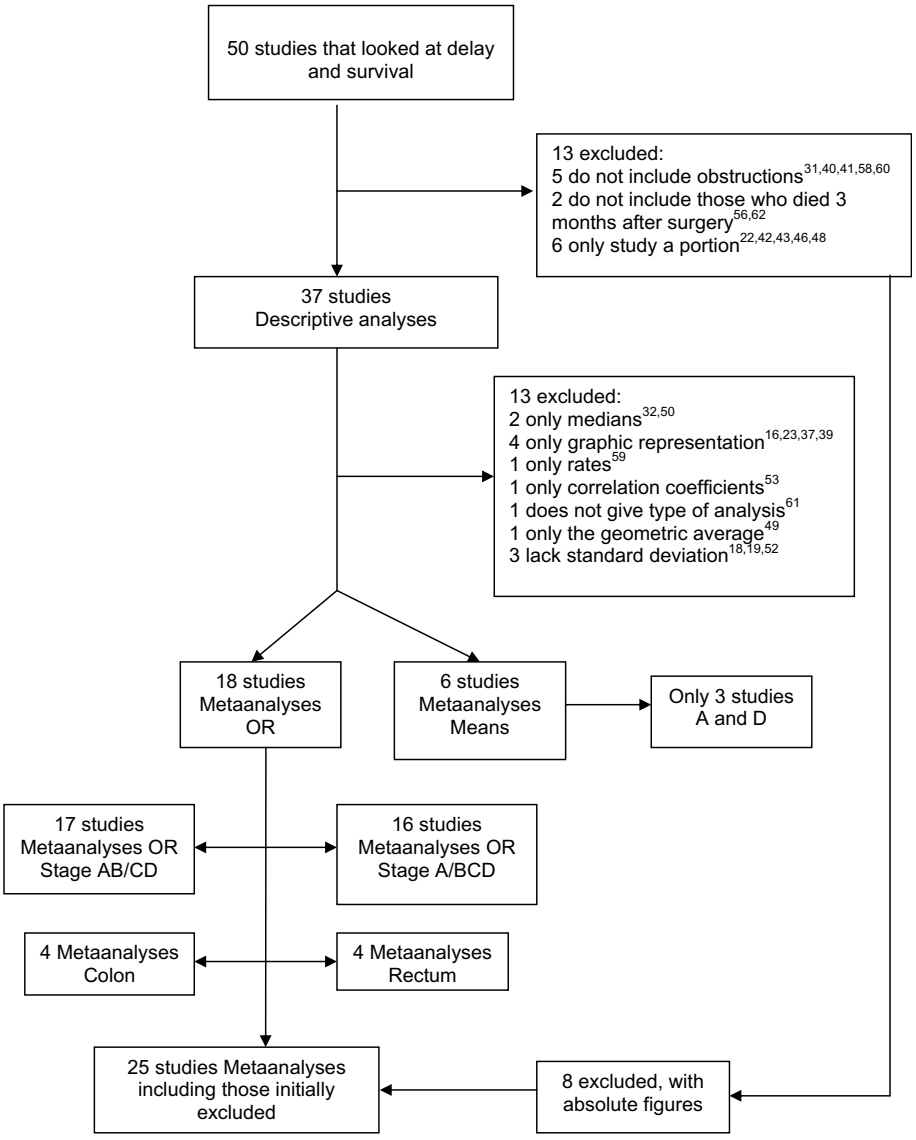

Fig. 1 – Summary of studies that were excluded.

or confined to patients amenable to surgery). Great variability was noted in connection with the type of classification used for disease stage and the type of measurement used for the delay, such that when the original Dukes classification (A, B and C) was used and when cut-off points for delay were greater than 3 months, no association was ever noted between delay and disease stages.

To perform the meta-analysis, 13 studies had to be excluded (Fig. 1) because they did not provide the absolute figures that were required for calculating ORs. Of these studies, 11 showed no association between delay and disease stages;[16,18,23,32,39,49,50,52,53,59,61] one showed an association between a longer delay and diagnosis at an earlier stage,[19] and one showed an association between a shorter delay and diagnosis at less advanced stages.[53]

Meta-analysis was performed by calculating ORs based on 17 studies that included 5209 patients. The wide variations between studies have been corroborated by means of Dersimonian's and Laird's test ($P = 0.0001$). The combined OR was 0.98 (95% confidence interval (CI): 0.76–1.25). Fig. 2 shows the forest plot. The result remains the same even after eliminating the studies one by one. The results obtained when Begg's and Egger's tests were applied ($P = 0.718$ and $P = 0.2591$, respectively) support the absence of publication bias.

3.1. *Sensitivity analyses*

(1) In four of the 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 obtained were not statistically significant, but showed the opposite signs: 0.86 (95% CI: 0.63–1.19) for the colon (Fig. 3) and 1.93 (95% CI: 0.89–4.219) for the rectum (Fig. 4).

(2) The meta-analysis was repeated using a different definition of early- and late-stage disease. In this case, only stage A was considered to be early-stage, and

Table 3 – Characteristics of studies on delay, excluding those with very restricted samples or that studied only a portion of the delay

Variable	Number of studies	Sample size	Results		
			>delay <stage	<delay <stage	No association
Continent					
Europe	26	9498	3	6	17
America	4	819	0	0	4
Australia	4	1003	1	0	3
Asia	3	679	0	1	2
Site					
Colorectal	24	5755	4	3	17
Colon and rectum separately	8	2725	0	3	5
Colon	2	3011	0	0	2
Rectum	3	508	0	1	2
Year					
From 1968 to 1990	20	4500	3	4	13
From 1991 to 2000	10	5784	1	1	8
From 2001 to 2006	7	1715	0	2	5
Setting					
Hospital-based	33	8420	4	6	23
Population-based	4	3579	0	1	3
Sample characteristics					
Not restricted	19	8266	3	5	11
Amenable to surgery	18	3733	1	2	15
Sample size					
<300	25	3986	3	4	18
300–499	8	2995	0	1	7
500–999	3	2049	1	2	0
1000 or >	1	2969	0	0	1
Source of information					
Hospital clinical history	16	6849	2	0	14
Interview	12	2896	1	2	9
Primary care clinical history	3	614	0	1	2
Not given	6	1640	1	4	1
Definition of delay					
Global until time of diagnosis	18	6987	3	4	11
Global until time of treatment	19	5012	1	3	15
Measures of delay					
Means	9	1422	2	1	6
Medians	3	518	0	1	2
<1 month and other intervals	8	3029	1	2	5
<2 months and other intervals	4	1648	0	2	2
<3 months and other intervals	9	3799	1	1	7
<5 months and other intervals	1	321	0	0	1
<6 months and other intervals	2	384	0	0	2
Quartiles	1	349	0	0	1
Classification of stage					
Dukes' original	6	1380	0	0	6
Dukes' modified	17	4247	2	3	12
Dukes' simplified	3	1097	0	1	2
TNM	3	3833	1	0	2
UICC	1	70	0	1	0
ACP	2	255	0	1	1
Localised–regional–disseminated	5	1117	1	2	2
Measures of delay by stage					
Means	10	1750	2	1	7
Medians	2	721	0	0	2
Frequencies	15	7335	1	5	9

(*continued on next page*)

Table 3 – (*continued*)

Variable	Number of studies	Sample size	Results		
			>delay <stage	<delay <stage	No association
Correlations	3	475	0	1	2
Graphics	4	1061	0	0	4
Absolute figures	2	371	1	0	1
Not given	1	286	0	0	1
Multivariate analysis					
Yes	2	646	0	1	1
No	35	11,353	4	6	25
Confidence interval					
Yes	7	5723	1	2	4
No	30	6276	3	5	22
Total	37	11,999	4	7	26

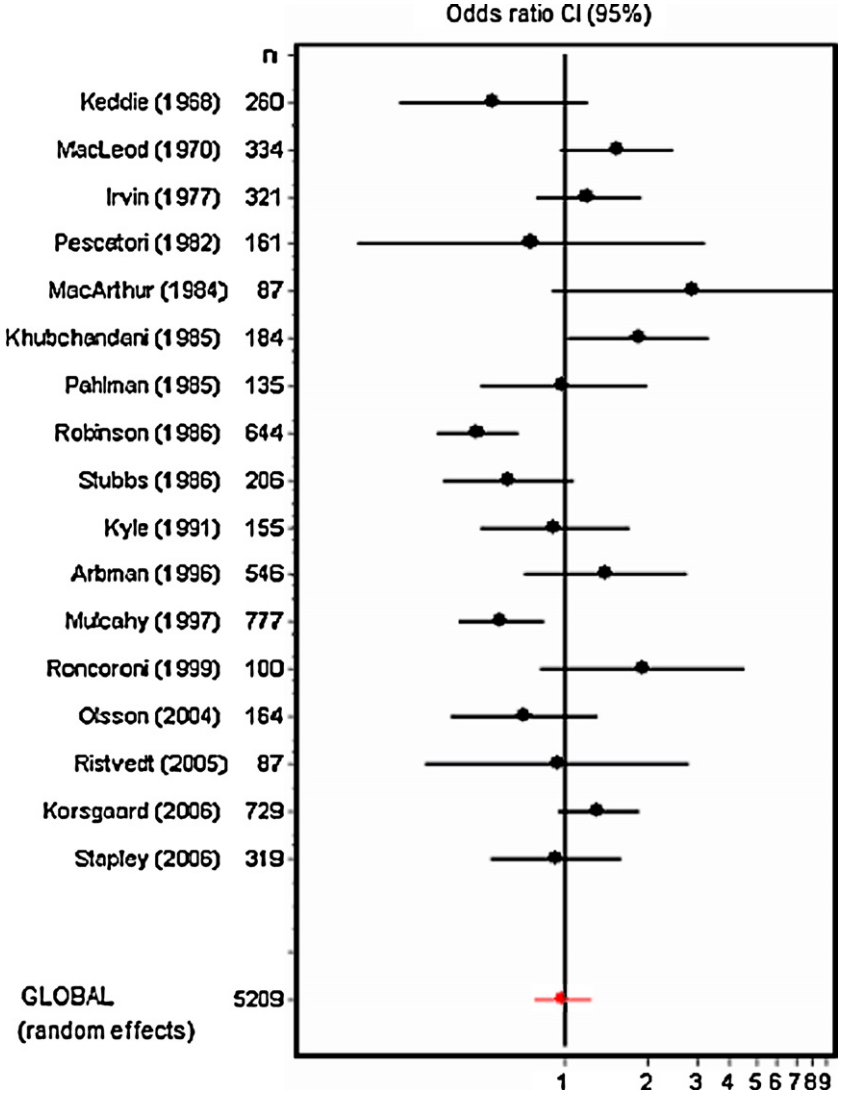

Fig. 2 – Forest plot global.

the others to be late-stage disease. In this case, two studies had to be eliminated because they dealt with stages A and B as a whole, but it was possible to add one other study that compared stage A with all the other stages. Thus, in all there were 16 studies and a population of 4492 patients. A combined OR of 1.18 was obtained with the random effects model (95% CI: 0.85–1.63).

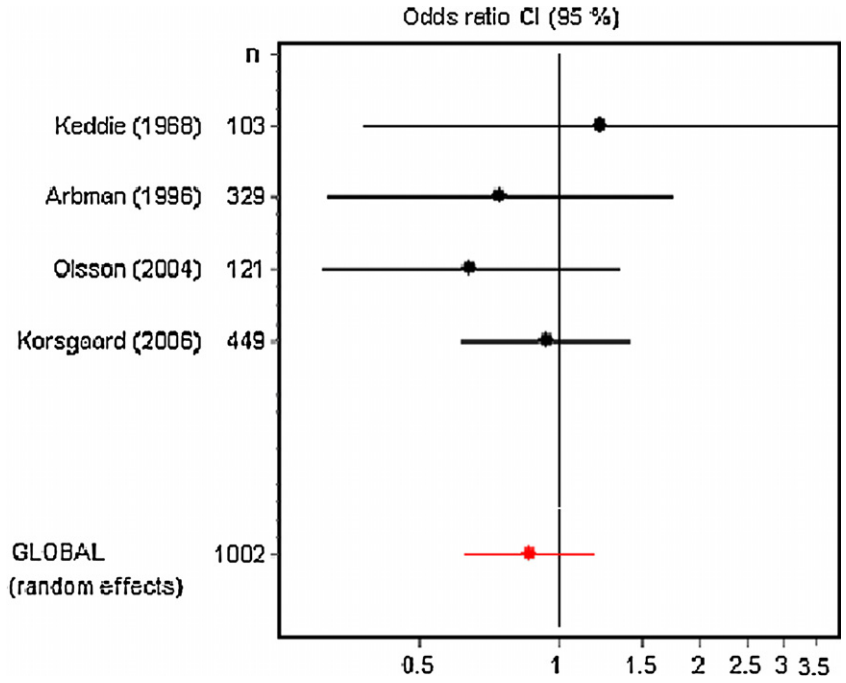

Fig. 3 – Forest plot, colon.

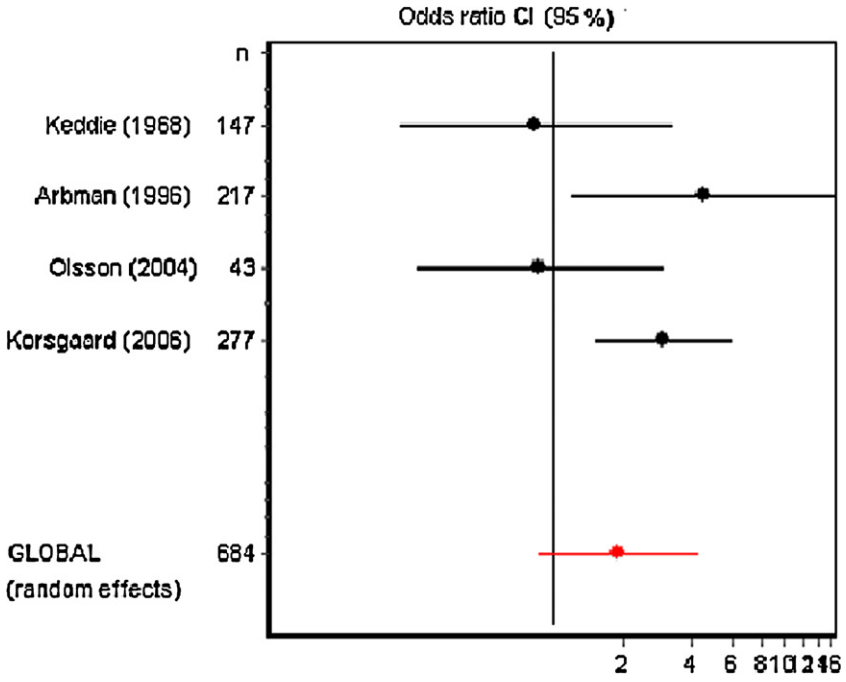

Fig. 4 – Forest plot, rectum.

(3) We tried to perform a meta-analysis with the studies that used means to measure the delay but we were unable to do so because out of nine such studies, only six gave the standard deviation, which is necessary to calculate the standard error, and of these six, only three used a classification that included stage D.

(4) Finally, we repeated the meta-analysis with the studies that were excluded initially. Of these studies, only eight provided absolute figures. We therefore had a total of 25 studies and a population of 9183 individuals, and we obtained a combined OR of 1.09 which was obtained with the random effects model (95% CI: 0.91–1.32).

4. Discussion

The results obtained point to a lack of association between the delay and disease stages at the time the colorectal cancer is diagnosed, although they do suggest the possibility of an opposite effect in the case of cancers of the colon and rectum. At the same time, several recommendations for future studies can be derived from the review performed.

The review has several limitations, one of them being the wide variability observed in several key elements, such as the units of measure used for the delay and the classification of disease stage. In terms of the units of measure for quantifying the delay, some studies used means, whereas others employed different cut-offs between 1 and 6 months that were chosen in a rather arbitrary way. To perform the meta-analysis we had to define, in a likewise arbitrary manner, the presence or absence of a delay with respect to the first cut-off point used. This method was already employed in the review mentioned earlier on delay and survival,[8] whose results were similar to those obtained when the first cut-off point was uniformly fixed at 6 months. This indirectly supports the hypothesis that in cancer, the symptomatic phase is only a small portion of the natural history of the disease and that 1, 2 or 3 months make little difference in the overall history.[37] In fact, most colorectal cancers, if not all, begin as adenomas, according to Fearon and Vogelstein adenoma–carcinoma sequence theory,[65] and it is felt that the transformation of these into cancer takes anywhere between 5 and 15 years.[66]

In terms of stage, the great majority of the classifications used show that there is no ideal classification method. Dukes himself modified his initial classification of rectal cancers, based on the degree of tumour spread[67] in subsequent publications,[68] as have other authors as well, such as Turnbull[69] and Astler and Coller.[70] On the other hand, the Union Internationale Contre le Cancer (IUCC) [International Union Against Cancer] and the American Joint Committee for Cancer (AJCC) have established other classification systems that were later brought together in the TNM scheme, which is the classification recommended by the experts.[71] In the review performed, we have seen that the most widely used classification methods are Dukes' modified schemes, mainly the one that comprises four stages (A, B, C and D). Some countries, such as Australia, use classifications of their own;[34,38] others use Dukes' simplified criteria[16,23,28] or even *ad hoc* classifications into localised, regional and disseminated cancer.[25–27,33,49,50] The TNM scheme was used in only five studies.[32,35,40,59,64] The hypothesis can be put forward that the classification scheme used may have an influence on the relationship between delay and disease stages. Assessing this relationship using the TNM scheme would be advisable in future studies.

In view of all of the above, we feel it may be worthwhile for future articles to provide as much information as possible: for the length of the delay, provide the mean, median, and standard deviation, as well as cut-offs; for classifying disease stage, use Dukes criteria as well as the TNM scheme, and always include tables showing absolute figures. This will make it easier to compare studies and to include them in future syntheses of research results.

In our review, we found that most of the studies used very small samples, confined frequently to patients with operable tumours and analyse mostly colon and rectal tumours separately. Another remarkable feature is the scarcity of studies that look at the independent effect of other confounding variables. In examining the potential association between delay and disease stages, only age, sex, and, in one case only, tumour site, socio-economic level and co-morbidity were considered. We find it surprising that no study looked at the degree of tumour differentiation, a variable that, according to Dukes, may reflect the pace of tumour growth, while disease stage may be a measure of the limits attained by such growth.

The degree of tumour differentiation is not usually associated with the delay when colorectal cancers are studied as a whole,[18,31,36] with few exceptions.[39] On the other hand, when they are looked at separately, in the case of colon cancer, a shorter delay is associated with lesser tumour differentiation,[51,56,57] although the association disappears when intestinal obstructions are excluded.[51] In the rectum, well-differentiated tumours are more common when the delay is short (less than 3 months), whereas with longer delays, most tumours are moderately differentiated, and undifferentiated tumours are seldom seen in patients with lengthy delays (1 year or longer).[61] On the other hand, Dukes found an association between the degree of tumour differentiation and disease stage in his initial classification.[68] Yet in another study, which used Astler and Coller classification for determining disease stage, no association was noted between the two variables.[72] As may be the case when dealing with disease stage, one possible explanation for those differences may be the type of classification used. The first one employed was the one developed by Broders,[71] who established four grades based on the percentage of differentiated tumour cells. Dukes[67] established another that comprised of three grades which was based on the cellular arrangement, and subsequently others, such as Jass',[73] have been described. In our review, the majority of studies that include this variable do not give the type of classification used. Despite the opinion of some experts who reject this variable because it is subjective,[74] we feel that the degree of tumour differentiation may be a confounder and that its effect should be further explored in future studies.

An opposite trend appears to be at work in the relationship between delay and disease stages in the case of cancers of the colon and rectum whenever it has been possible to study them separately, despite the fact that neither of the two results has been statistically significant. In the case of rectal cancer, a shorter delay has been associated with less advanced disease, while in the case of colon cancer, paradoxically, a longer delay has appeared to be associated with less advanced disease. We believe these results are compatible with what is currently known about the natural history of cancers of the colon and rectum. Whereas in rectal cancer there is more uniformity in how symptoms present, with the so-called 'distal cluster'[37] – rectal haemorrhage and changes in bowel movements, along with rectal pain or tenesmus – colon cancer usually begins insidiously with non-specific complaints,[55] but in a minority of cases symptoms appear abruptly with intestinal obstructions that end up in the emergency room. It has been shown

that in these cases, in which the delay is minimal or non-existent, the prognosis is worse.[75]

At the same time, some studies have shown that the percentage of adenocarcinomas with concomitant adenomas and, therefore, with adenocarcinomas that presumably arose from adenomas, varies according to tumour site and sub-site, that is, not so much between the colon and the rectum, but even between the proximal and distal colons: 5.7% for the proximal colon; 14.3% for the distal colon and 17.7% for the rectum.[76] It has also been suggested that adenomas in the rectum may be more aggressive than those in the colon, as they appear to show severe dysplasia in a much greater percentage of cases.[77] The transformation from adenomas to adenocarcinomas requires the accumulation of a certain number of alterations that may be genetic, hereditary or caused by environmental agents, such as diet. There is some evidence to the effect that the frequency with which these alterations are found in the colon and rectum is different, which suggests the presence of different genetic pathways for the development of these cancers.[78] On the other hand, survival for colon cancer in men and women is greater than it is for rectal cancer,[5] a fact that has been linked to a greater frequency of hereditary cancers in the colon, which carry a better prognosis.[74]

Finally, aetiologic studies also show some differences between the colon and rectum, whether they explore the role played by dietary components,[79,80] alcohol intake[81] or physical activity.[82,83]

In short, we can conclude that

- When colorectal cancers are taken as a whole, there appears to be no association between diagnostic delay and disease stage at the time the diagnosis is made.
- However, when cancers of the colon and the rectum are studied separately, there may be an opposite effect in the sense that a shorter delay is associated with more advanced disease in the case of colon cancer, whereas it is beneficial in the case of rectal cancer, since it allows for diagnosis at an earlier stage.
- Future studies evaluating the effect of delay on disease stage should include large and unrestricted samples to solve those methodological problems detected in this review. The degree of tumour differentiation should be taken into account, since it may act as a confounder.
- A consensus document should be developed for further studies on diagnostic delay.

Conflict of interest statement

None declared.

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