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Time to diagnosis and stage of symptomatic colorectal cancer determined by three different sources of information: A population based retrospective study

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ABSTRACT

Background: Survival rates from colorectal cancer (CRC) are highly variable in Europe. This variability could potentially be explained by differences in healthcare system delays in diagnosis. However, even when such delays are reduced, the relationship of the diagnostic interval (time from presentation with symptoms to diagnosis) with outcome is uncertain.
Methods: A total of 795 patients with CRC from 5 regions of Spain were retrospectively examined in this population-based multicenter study. Consecutive incident cases of CRC were identified from pathology services. The total diagnostic interval (TDI) was defined as the time from the first presentation with symptoms to diagnosis based on 3 different sources of information: *(i)* patient-recorded data (PR-TDI) by interview, *(ii)* hospital-recorded data (HR-TDI), and *(iii)* general practitioner-recorded data (GPR-TDI). Concordance correlation coefficients (CCCs) were used to estimate the agreement of 3 different TDIs. The TDIs of patients with different stages of CRC were also compared using the Kruskal-Wallis test.
Results: The median TDI was 131 days based on patient interview data, 91 days based on HR data, and 111 days based on GPR data. Overall, the agreement of these TDIs was poor ($CCC_{PRvsHR} = 0.399$, $CCC_{PRvsGPR} = 0.518$, $CCC_{HRvsGPR} = 0.383$). Univariate analysis indicated that the TDI was greater in those with less advanced CRC for all 3 methods of calculation, but this association was only statistically significant for the HR-TDI ($p = 0.021$).
Conclusion: There is no evidence that patients with more advanced CRC have longer TDIs. In fact, we found an inverse relationship between the TDI and CRC stage, an example of the "waiting time paradox". This association may likely be due to the presence of unmeasured confounders as the stage when symptoms appear or the tumour aggressiveness.

1. Background

Colorectal cancer (CRC) is the second most common cancer and the second leading cause of cancer deaths in Europe. The five year relative survival rates in Europe are 57% for cancer of the colon and 55.8% for cancer of the rectum [1]. Thus, there is an urgent need to improve the outcomes of patients with CRC.

Most patients with CRC are diagnosed after presentation with symptoms [2]. Many countries have implemented standardised

Abbreviations: CRC, colorectal cancer; GP, general practitioners; GPR-TDI, general practitioner-recorded data; HR-TDI, hospital-recorded data; IQR, inter-quartile range; PR-TDI, patient-recorded data; TDI, total diagnostic interval; TNM, tumour, node, metastasis.

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pathways for patients with suspected cancer to ensure fast diagnosis of patients suspected of having CRC, because early treatment can help to improve outcome. However it is unclear whether earlier diagnosis leads to more favourable outcome. Prospective randomized trial data in this area is lacking [3] because of ethical and logistical challenges, and most of the published literature on this topic is from observational studies. Data from observational studies could be misleading because of information bias or confounding [4,5]. Other methodological limitations are the significant heterogeneity in how the researchers define delay of diagnosis, stage classification, and source of information on symptom onset [6–8]. These previous studies are mainly based on three sources of information: hospital records, general practitioner records, or patient interview.

Systematic reviews of observational studies of CRC have produced some discordant and surprising results [6–9]. For example, some studies have shown that the diagnostic interval (time from presentation with symptoms to diagnosis) is inversely related to survival [10–15]. This relationship is an example of the "waiting time paradox", and was also described for gastric cancer, cervical cancer, breast cancer, oral cancer, and lung cancer [16]. The waiting time paradox refers to a scenario in which patients with shorter diagnostic intervals have more advanced disease and poorer outcomes.

The aims of this study are to determine the diagnostic intervals for the diagnosis of CRC by using three different sources of information and to analyse the relationship of CRC stage with the diagnostic interval according the source of information.

2. Methods

2.1. Study design

We conducted a multicenter, cross-sectional study in 5 regions of Spain and enrolled 795 consecutive incident cases with symptomatic CRC. All patients were diagnosed with CRC based on the International Disease Classification-9 (153–154), were identified through the pathology[1] services of 9 public hospitals (Son Dureta Hospital, Son Llatzer Hospital, Manacor Hospital, Can Misses Hospital, Valencia Clinic Hospital, Mar Hospital, Miquel Servet Hospital, Zaragoza clinic hospital, Juan Canalejo Hospital) from September 2006 to September 2008, and were registered with general practitioners (GPs). Patients younger than 18 years-old and those considered as prevalent or recurrent cases, with multiple tumours, and diagnosed in private hospitals were excluded.

2.2. Data collection

Once an eligible patient was identified, the study coordinator contacted the patient specialist to arrange recruitment and an interview. Patients were contacted during the inpatient stage or during the oncology visit by the surgeon or oncologist, who then invited them to participate. The interview was scheduled by the study coordinator and employed a structured questionnaire during the inpatient stage, oncology visit, or at home by a trained nurse or GP if necessary. All patients provided informed consent for study participation. After the patient interview, research assistants reviewed hospital and GP clinical records. These methods were described in more detail previously [17–19].

Socio-demographic characteristics were collected during the interview. Each patient was asked how long he/she had been feeling unwell. Symptoms spontaneously reported by the patient were considered to be initial symptom (s) and the date was recorded. If the patient remembered the exact date when symptoms occurred, this date was recorded; if the patient could not remember the exact date, but could only estimate the date, then the estimated date was recorded. Afterwards, the interviewer asked patients if they had any of the symptoms listed in a checklist. When questions on symptoms were finished, the interviewer recapitulated all of the recorded data and obtained patient agreement. Patients were also queried about their perceptions of the seriousness of symptom(s) and could respond as "alarmed", "serious", "not serious", or "don't know". These last two categories were combined for the data analyses.

Hospital records were reviewed after the interview. After identification of the date of diagnosis from the pathology report, the research assistant reviewed the records to identify the dates at which the patient first reported symptom(s), TNM stage, tumour location, emergency room admission, and diagnosis (date of first pathological report).

The research assistants reviewed the GP records from 2 years prior to the date of diagnosis to identify the first contact date with CRC symptom(s), type of referral, and diagnosis suspicion in a referral letter.

2.3. Diagnostic intervals

The "patient-recorded total diagnostic interval" (PR-TDI) was the date from when the patient first experienced symptoms (based on patient recall) to the date of diagnosis. The "GP-recorded total diagnostic interval" (GPR-TDI) was the date from the first registry of symptoms in the GP records to the date of diagnosis; this only included symptomatic patients who contacted GPs for symptoms of CRC. The "hospital recorded total diagnostic interval" (HR-TDI) was the date from when symptoms were first registered in the hospital records to the date of diagnosis.

2.4. Statistical analysis

The time intervals are presented as medians and inter-quartile ranges (IQRs) and categorical variables as proportions. The Mann-Whitney *U* test and the Kruskall-Wallis test were used to assess the relationships of the TDIs with patient characteristics, tumour location, type of symptoms, presence of obstruction, patient perception of the seriousness of symptoms, mention of CRC suspicion in the referral, referral urgency, presence of an emergency room visit, and CRC stage. Afterwards, we performed a sensitivity analysis to investigate the impact of time intervals on tumour stage in subsamples of patients, in which PR-TDI and HR-TDI, PR-TDI and GPR-TDI, and HR-TDI and GPR-TDI were captured. We used cumulative incidence plots to assess the association of CRC diagnosis and total diagnostic delay based on 3 different sources of information.

We calculated the strength of the agreement between TDIs by Lin's concordance correlation coefficient [20] (CCC), which provides information about the precision and accuracy of 2 methods. The CCC considers biased differences between 2 different measurements. It is generally considered that 2 methods have good agreement if the CCC is greater than 0.95 and moderate agreement if the CCC is between 0.95 and 0.90.

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