DIAGNOSTIC DELAY IN COLORECTAL CANCER

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ABSTRACT
Background: Colorectal cancer is the second most frequent tumour in developed countries. Survival in colorectal cancer depends mostly of disease stage at the time of diagnosis; it seem reasonable therefore, that those individuals with symptoms or signs suspicious of colorectal cancer should be investigated without delay in order to have an early diagnosis. Many factors intervene in interval duration between symptoms onset and diagnosis; both patient and health care service. This study was designed to: 1) Describe the diagnostic process of colorectal cancer (CRC) from the onset of the first symptom to diagnosis and treatment. 2) Establish the time interval from initial symptom/s to diagnosis and treatment, globally and considering patient and doctor's delay. Doctor's delay will also be described considering the one due to family physician and those attributed to hospital services. 3) Identify the factors related with defined types of delay. 4) To asses the concordance about the onset of the first symptom/s between information included in primary health care and hospital clinical records.
Design: Descriptive study, co-ordinated, with 5 participant groups of 5 different Spanish regions. Setting: Balearic Islands, Galicia, Catalunya, Aragón and Valencia Health Districts with a total of 8 acute public hospitals and 140 primary care centres.
Subjects: Incident cases of CRC during the study period. Cases will be identified from hospitals pathology services. A sample size of 896 subjects has been estimated, 150 subjects for each participant group.
Information will be collected through patient interview, primary health care and hospital clinical records with a questionnaire and a separate card for personal identification data.
Measurements: Patient variables (socio-demografic variables, familiar cancer, symptom perception, family doctor confidence) about tumour (tumour site, histological type, grade and stage); on symptoms (data of onset, type and number of symptoms); health
system variables (number of contacts with family physician, type of referral, content of the referral, hospital services which attended patient, investigations and results) and different delay intervals (global, patient delay, family physician and hospital delay).

Discussion: In order to obtain a non restricted sample of colorectal cases we have minimised selection risk identifying the patients from pathology services. A more potential constrain could be associated to information sources based on clinical records. Due to inherent features of co-ordinated studies it is very important to make special effort in standardising collection of information.
Background

Colorectal cancer (CRC) is one of the most common cancers in western countries. In Spain, cancer incidence and mortality rates are situated roughly, half way in comparison with those of other European countries (1). In terms of cancer survival, data published in EUROCARE show that Spain is above the European average for both men and women and is greater for colon cancer than for rectal cancer (2).

Survival in Colorectal cancer depends mostly of disease stage at the time of diagnosis. Most of the patients will be alive after five years if the tumour has not reached the intestinal wall (stage I). This figures reach a 60% if tumour has invaded lymph nodes and only a 5-15% if the neoplasm is found in stage IV. (2) It seems reasonable therefore, that those individuals with symptoms or signs suspicious of CRC should be investigated without delay in order to exclude the existence of CRC as early as possible. However, many aspects of the association between delay of diagnosis or treatment and stage are poorly understood. It has been suggested that delay of diagnosis or treatment may be predictors of the stage and survival of colorectal cancer ; but the results of the studies are controversial (3-8). The majority of studies on CRC are not recent, dealt with small and restricted sample sizes and were limited to hospital settings.

Most studies use the term delay to describe the time elapsed between onset of the first symptom to diagnosis or treatment. Conceptually, diagnostic delay in cancer is a complex process conformed by patient behaviour; doctor’s attitude; response of the health system; biology of the tumour cells, and interaction between host and tumour.

Studies on delay tend to make a distinction between patient and health system delay:

1. Patient Delay. There are a number of reasons why a patient, facing a sign or symptom suspicious of malignancy, may decide or not to visit a doctor. The patient could not be aware of the importance of symptoms (9), or feel embarrassed to consult about them (9), did not relate them with the disease (10), or fears a possible cancer diagnosis (11). A family history of cancer together with a negative attitude to the medical profession can also be a reason for delay (12) as it is a previous history of anxiety or depressive illness (13) Other factors such as age, civil and social status, mistrust in doctor or simply, a lack of time to visit a physician has also been described (14-15). Among type of symptoms, anaemia is the most frequent finding associated with longer delay (16-17) and multiple symptoms, with shorter delay (13). Equally it has been observed that the
presence of a constitutional syndrome is associated with a diagnosis made in the hospital emergency department while low abdominal symptoms are more common in patients with elective surgery (18).

2. Family doctor delay: general practitioner plays an active role in cancer diagnosis with a participation in nearly 63% of cancer cases (19). His style of practice is important in recognising CCR. In a study on family doctors’ clinical management of patients with gastrointestinal symptoms, Springall et al observed that a third of them didn’t have a physical examination. Digital rectal examination was performed in less than half of all patients and at least ninety percent of all hospital referrals, failed to include the primary care examination findings (20). Unspecific symptoms, no routine rectal examination and patient reluctance of rectal exploration may increase delay (21-22).

3. Hospital delay: Factors described as possible contributors to delay include specialist referrals’ waiting lists, poor co-ordination, complementary examinations. Porta et al noted, that 65% of patients affected by gastrointestinal tract cancers were diagnosed at the hospital’s emergencies department. Moreover, half of them, had been visiting their general practitioner on several occasions with symptoms related to CRC (18).

It becomes clear that more information is needed on the effects of delay on CRC. There is also a poor understanding about the factors linked to it, regardless of whether they are related to the patient, to the family doctor or to the hospital setting. In Spain, several Regional Health Plans have highlighted problems in continuity of care and advocate for a reduction in time interval between suspicion of cancer and diagnosis or treatment. In order to achieve these objectives it is essential, firstly to know the characteristics of the CRC diagnostic process. Secondly, it is important to qualify the delay that may occur at various stages. Finally, it is also necessary a better understanding of factors associated to each type of delay.

**Objectives**

1. To describe the diagnostic process of CRC from the onset of the first symptoms until diagnosis and initial treatment in terms of:
   - Initial symptom/s; other symptoms appearing prior and during the diagnostic process.
   - Family doctor participation in diagnosis: Proportion of cases diagnosed by the family doctor; visits per patient, physical examination; complementary tests requested according to the nature of symptoms; type of referral to specialist and clinical information included in the referral.
Hospital specialist diagnostic procedures: hospital department, type of hospital; complementary examinations and its results (true positives and false negatives).

2. To establish the time intervals between the first symptom and diagnosis-treatment:
Patient delay: Time interval from the onset of first symptom/s of CCR and first contact with a doctor.
Health system delay: This delay is separated into three elements: time elapsed between first contact with a doctor and referral to an specialist or emergency department; from specialist visit to diagnosis and time interval between diagnosis and treatment.

3. To identify factors related to:
Patient: sociodemographic; patient referred symptoms; attitude towards symptoms; confidence in the doctor; and family history of cancer.
Health system: - primary care (physical examination, clinical assessment by family physician) - specialist care (access to examination tests, referral paths, type of hospital, type of department, number and type of complementary examination tests and its results)

Secondary objectives:
4. To evaluate the reliability and thoroughness of information about symptoms from patient interview, primary care and hospital records.
5. To describe the variability of delay between the areas and hospitals included in the study.

Methods

Study design
Descriptive and multicentric study participating 5 health districts of Spain (Balears, Galicia, Catalunya, Aragón and Valencia) including 8 acute public hospitals and 140 primary health centres. Information will be collected from medical records and structured interviews with patients.

Subjects
Incidence cases with histologically verified CRC (CIE9 153 y 154) diagnosed during 2006-07 within the study hospitals; being registered with a family doctor in health centre included in the study.
Exclusion criteria: Prevalent cases and/or recurrences; cases of multiple cancer and cases diagnosed at private hospitals.

Cases will be identified by hospital pathologists. Once identification is complete, the doctor responsible for the patient will be contacted and informed of the possible patient inclusion. Afterwards, inclusion and exclusion criteria will be verified in the HC clinical record. Informed consent will be requested from the patient. Interview will be carried out mainly during the patient’s hospital stay, otherwise at home.

Sample size:
The sample size necessary for the whole multicentric project would be of a minimum of 896 individuals to achieve the study objectives with an accepted 5% alpha error and an accuracy of a tenth of the observed relative frequency of different variables. Moreover, the selected sample size will obtain an estimate for symptoms duration, in spite of the usual dispersion of a ‘time’ variable (usually a standard deviation over the mean). Also, this sample size will permit to achieve objective number 3 in order to assess if delay is related described factors for an alpha error <=0.05 and a power >= 80%. Having at least 150 cases in each region, will allow a precise estimation of geographical variations.

The number of persons included must be increased to 1,000 subjects as secondary and often incomplete information from primary care (PHC) and hospital (HC) clinical records will be collected.

Information:
A pre-inclusion patient form will be designed to hold patient pathology results together with exclusion criteria. A data collection book (DCB) will be prepared to include information about interview, primary health care and hospital clinical records. A pilot study with 15 patients in each sub-project will be undertaken in order to standardise data collection and solve any conflicts. In that sense, we will also carry out a training workshop for field workers and interviewers. Patient interview will be centred mainly on CCR symptom/s, perceived attitude with initial symptoms and demographic data. As described by Belloc et al (23), the patient will be asked for how long has been feeling unwell and which type of symptom/s he noted. The symptom spontaneously referred by the patient will be considered the first symptom/s in accordance to the patient and date recorded. The patient will be request to refer any additional symptoms summarised in a check-list. Symptoms perceived up to 2 years prior the first consultation will be
considered. Non symptomatic patients will be recorded as a casual finding. Information on examination test dates, results and clinical departments involved, will be collected by reviewing medical records. Variables are summarised in table 1. The study was approved by the Clinical Ethics Committees of each participating region.

**Statistical analysis**

A database will be built with a unique numerical case code for each patient and checked for errors. Identifiable patient information will be kept dissociated. Each participating group will periodically send the patient data collection book to the co-ordinator node for centralised data entry. Number and reason for excluded and missing cases will be given.

**Objective 1.** A descriptive analysis of the key variables of the colorectal cancer diagnosis process will be carried out presenting frequency distribution and CI 95% as well as mean and median measures.

**Objective 2.** It will be detailed total time delay; patient and health system delay as well as their contribution to total delay.

**Objective 3.-** Relationship between different types of delay and the observed variables will be evaluated. The Chi-Square test will be used for the qualitative variables, and either the Student t test, Anova or non parametric tests for quantitative variables. In order to assess the effect of the predictive variables on delay times, a survival analysis will be performed as proposed by Latour (24). In contrast with follow up studies measuring survival, in the proposed study there will not be censored data. The survival curves will be obtained by the Kaplan Meyer method using the Log-Rank test to compare curves. To assess the independent effect of variables in delay times, a proportional risk analysis will be done using Cox regression. At the same time, it will be considered the adequacy of performing a multiple level analysis, to evaluate the effects due to hospital centre and District Health Authority. Analysis also will be carried out separately by colon and rectum.

**Objective 4.** The thoroughness of symptom information given by patients will be compared with information contained at the PHC and HC clinical record and a frequency distribution of variables in each of the different sources of information will be presented.

**Objective 5.** Evaluation of the variability of different delay intervals through comparison median times and the inter-quartile range for the considered variables.
Moreover for each variable it will also be estimated the proportional time variance of those areas and hospitals with longer and shorter delay and a graphical analysis.

Discussion
We have minimised the selection risk by identifying study cases from pathology reports instead of including them at admission for surgery. In Spain the percentage of histological confirmation in the CCR is greater than 96%. Nevertheless it is still possible that some cases are not included if they have no biopsy results due to either very advanced age or because of their severe ill-health. A potentially more important constraint could be associated to the information sources based on medical records. Use of secondary information could increase the risk of missing data for some variables. Nevertheless, we consider that the patient interview strengthen comprehensiveness of information. Due to the inherent features of co-ordinated studies it is very important to make a special effort in standardising data collection. Different observers in the different participating regions can bring about reproducibility problems.
Competing interests

The authors declare that they have no competing interests.

Authors contributions

ME, MR, EC, JLL, AR, participated in the design of the study SP, JMS, JMC, LG reviewed the study protocol and made suggestions that improved the design. All of them are involved in the management of the study. ME, MR, EC, JLL draft the manuscript. All authors read, revised and approved the final manuscript.

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References

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Table 1.- Study measurements

**Patient**
Age, gender, civil status, education, family history of cancer, symptom perception, confidence in the family doctor, and number of consultations until the first contact and reason for it.

**Tumour**
- Site, histological grade, TNM at diagnosis.

**Clinical:**
- First symptom, data of the first symptom and other symptoms.

**Delay intervals:**

**Patient-delay:**
- Time elapsed from the date the patient perceived the first symptom until the date of the first contact with a doctor as a result of the first symptom/s.

**Health system-delay.** This delay distinguishes the following phases:
- Time elapsed between the first contact with the health system (consultation with the family doctor, specialist, or emergency department) and until the date of referral to a specialist.
- Time elapsed between referral to a specialist or emergency department and until the diagnosis. In this context diagnosis is understood as the date of the biopsy or direct surgery if that was the case.
- Time elapsed between diagnosis and treatment. In this context we consider surgical treatment. Failing on that chemotherapy or palliative care treatment as the first option.

Total delay: Sum of all previous delays. There will be a distinction between diagnostic and therapy delay.

**Health system.**
- Health professional who attended the patient at the first visit: Family doctor or specialist including which speciality.
- Teaching versus non-teaching primary care centre; urban versus rural ones and receiving hospital. – Hospital service that attended the patient in the various contacts during the diagnostic process.
- Number of consultations to the family doctor; to primary care emergency services; and to the specialist since the first contact. Consultations cancelled with family doctor and specialist.
- Complementary examinations done at the first visit: rectal exam; abdominal palpation; ultrasound; blood tests; X Ray films. Delay duration for each of the complementary tests. - Request and date of complementary tests at each contact prior to diagnosis. Results of complementary tests in order to exclude false negatives.
- Type of referral done by the family doctor to the specialist: preferential; programmed; emergency department. Diagnostic assessment and referral details in terms of presenting clinical picture, physical examinations.