

Do Patient Delay and Diagnostic Delay Influence Long Term Survival in Patients with Gastric Cancer?

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ABSTRACT

Background & Aims: Gastric cancer is one of the most common malignancies, with an aggressive evolution and a poor long-term prognosis. No screening program is available in Europe for this pathology; therefore, the delay from the appearance of the first symptom until the initiation of treatment might influence the prognosis of gastric cancer patients. We aimed to investigate the impact on the prognosis of the delay in the presentation and diagnosis in patients with gastric adenocarcinoma.

Methods: Our study is a retrospective, single-center, observational cohort study, based on patients diagnosed with gastric adenocarcinoma and operated in our institution between 2013 and 2021. We have defined patient delay as the time from the onset of symptoms to the first encounter with a health care provider and diagnosis delay as the time from the first consultation with a health care provider to the establishment of the final diagnosis.

Results: A total of 671 patients were included in our study. The survival rate at 5 years was 55% for the patients operated with curative intent and 7.4% for the patients operated with palliative intent. Patient delay and diagnosis delay were not correlated with the overall survival. A lower survival was observed for patients admitted through transfer ($p<0.001$) or the emergency department ($p<0.001$). No statistically significant relationship was identified between patient delay or diagnosis delay and the age, gender or area of origin of patients. Patients that experienced melena or hematemesis had a shorter patient delay, with a highly significant statistical relationship ($p<0.01$). Patients that experienced nausea, epigastric pain, palpable epigastric tumor mass or anorexia also had a highly significant statistical relationship between the symptoms and the patient delay interval.

Conclusions: The overall survival is not influenced by the patient delay or diagnosis delay. An earlier presentation was correlated with some specific exhibited symptoms: upper gastro-intestinal bleeding, abdominal pain, palpable epigastric tumor, nausea.

Key words: patient delay - diagnosis delay – diagnosis - cancer diagnosis - gastric adenocarcinoma - gastric cancer.

INTRODUCTION

The development of tumors, including gastric cancer, starts with a silent, asymptotically period; only after a certain period, that depends on the type of cancer, its histopathological characteristics and biological behavior, the progressive tumor growth generates clinical symptoms. Most cancers will present when symptomatic, this being applied to gastric cancer

as well, since no screening programs for gastric tumors are available in Western countries [1, 2].

The interval from the first symptom to the initiation of treatment is assessed and quantified differently between different studies, making it more difficult to interpret the current published literature [3]. The interval from symptoms to treatment can be divided in several parts, based on Olesen et al. [4] description: first, the “patient delay” interval consists of the time from the first symptom until the first contact with a health-care provider, the “doctor delay” is defined by the time interval from the patient’s first contact with a medical doctor until the proper investigations are initiated and the “system delay”, represents the time between the initiation of the investigations and initiation of treatment. Another

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classification, by Walter et al. [5], proposes four succeeding intervals: appraisal, help-seeking, diagnostic and pre-treatment. Regardless of the classification system used, cancer should be seen as an acute disease, underlining the fact that the evaluation of these delays and their impact should be treated as a very serious health-care problem.

A small delay is inevitable, but assessment of the influence of the delay in presentation and diagnosis is important in order to appreciate the need of applying direct measures, such as patient education, primary care evaluation and specialized investigations, to prevent unnecessary delays and improve patient outcomes. Also, especially primary care physicians should maintain awareness of the risk of cancer, maintaining a low threshold of suspicion [6, 7].

Gastric cancer is a major public health issue, being one of the most common diagnosed malignancies, responsible for the fourth leading cause of cancer related deaths worldwide. The five-year survival rate fluctuates between 10 and 30%, in Europe, most cases being diagnosed in advanced stages [8, 9].

The aim of our study was to investigate the impact on the prognosis of the delay in the presentation and diagnosis in patients diagnosed with gastric adenocarcinoma.

METHODS

Our study is a retrospective, single-center, observational cohort study, based on the hospital database. The study population is represented by patients diagnosed with gastric cancer, operated in the Surgical Department of the Prof. Dr. O. Fodor Regional Institute of Gastroenterology and Hepatology, between 2013 and 2021. Our study was approved by the Institution's Ethical Committee.

We included only patients with the final histopathological diagnosis of gastric adenocarcinoma, who underwent surgery either with palliative or curative intent. We excluded patients with other histopathological diagnoses and patients with insufficient or incomplete data regarding the variables of interest. In order to assure a uniform cohort and to avoid any variabilities in the evolution of the patient determined by the histopathology of the tumor, we decided to only address these cases with the final diagnosis of gastric adenocarcinoma.

Nine hundred thirty-two patients with gastric cancer were identified. After excluding patients with other histopathological diagnoses, 712 patients with gastric adenocarcinoma were selected. Due to insufficient data, 41 cases were excluded, and 671 patients were included in the final analysis.

Patient demographics (age, gender, residency - urban versus rural area), symptoms at presentation, type of admission (emergency, transfer, or appointment), tumor characteristics (histopathology, grade of differentiation, localization, staging), surgical intervention, date of the surgery, time of death, patient delay, diagnosis delay were registered. The last follow-up was in May 2021. Overall survival was defined as the time from the day of surgery to the time of death from any cause. Patient delay was considered the time from the debut of symptoms to the first encounter with a health care provider. Diagnosis delay was defined as the time from the first consultation with a health care provider to the establishment of the final diagnosis. The first contact of a patient with a health care provider was with

a general practitioner, in patients with non-urgent symptoms or with an emergency unit doctor if the patient was admitted through emergency settings. The final diagnosis was established after referral to a secondary care doctor (gastroenterologist, internal medicine doctor or general surgeon).

Statistical Analysis

Data analysis was performed using R 3.5.1. Normality of the distribution was assessed using histogram visualization and skewness and kurtosis assessment. For a variable to be considered normally distributed it had to have an absolute skewness and kurtosis under 0.5 and to have a histogram shape that was in accordance with those findings. Non-normally distributed variables were represented as median (quartile 1, quartile 3). Differences between two non-normally distributed variables were assessed using the eMann-Whitney-Wilcoxon rank sum test. Differences between three or more non-normally distributed variables were assessed using Kruskal-Wallis test. Correlation between two non-normally distributed variables was assessed using Spearman's test. Categorical variables were represented as an absolute number (percent). Survival analysis was performed using Cox proportional hazards. A p value under 0.05 was considered statistically significant.

RESULTS

The characteristics of the 671 patients included in our study are presented in Table I. The initial symptoms are shown in Table II.

The median patient delay was 2+/-3.18 months, with an average of 2.98 months. The median diagnosis delay was 0.5+/-1.73 months, with an average of 1.09 months.

The survival rate of the included patients was calculated separately whether the surgical intervention had curative [492 (76.0%)] or palliative [155 (24.0%)] intent. For the patients operated with curative intent, the survival rate at 1 year was 74.6%, at 3 years was 62.2% and at 5 years 55%. For the palliative intent group, the survival rate was 25.8% at 1 year, 11.6% at 3 years and 7.4% at 5 years. The average survival rate was 32.76 months.

Patient delay and diagnosis delay were not correlated with the overall survival ($p=0.817$, respectively $p=0.086$) when used as continuous variables. This was also the case when we used all possible cutoff values of patient delay to predict overall survival (Fig. 1).

Conversely, the association between diagnosis delay and overall survival seemed to become significant after a cutoff of more than seven months (Fig. 2).

The relationship between patient and diagnosis delay and overall survival on different subgroups of patients was analysed; no statistical significance on the curative intervention group ($p=0.575$ and $p=0.232$), on patients that underwent total gastrectomies ($p=0.277$ and $p=0.633$) or on patients that underwent subtotal gastrectomies ($p=0.114$ and $p=0.224$).

A lower survival was observed for patients admitted through transfer ($p<0.001$) or the emergency department ($p<0.001$).

No statistically significant relationship was identified between patient delay and the age ($p=0.862$) or area of origin

Table I. Study population

Variable		N, %
Gender	Male	450 (69.6)
	Female	197 (30.4)
Residency	Rural area	271 (41.9)
	Urban area	376 (58.1)
Surgery	Total gastrectomy	222 (34.3)
	Subtotal gastrectomy	259 (40)
	Superior polar gastrectomy	18 (2.8)
	Palliative	148 (25.7)
Tumor location	Subcardial	90 (13.9)
	Fundus	6 (0.9)
	Body	198 (30.6)
	Antral	261 (40.3)
	Combined and Other	92 (14.2)
Staging	0	5 (0.8)
	I	81 (12.5)
	II	111 (17.2)
	III	274 (42.3)
	IV	40 (6.2)
	Unknown	136 (21)
Grade of differentiation	G1	79 (12.2)
	G1/2	16 (2.5)
	G2	149 (23)
	G2/3	36 (5.6)
	G3	233 (36)
	Unknown	134 (20.7)
Type of admission	Appointment	501 (77.7)
	Transfer	55 (8.5)
	Emergency	89 (13.8)

Table II. Reason for admission

Variable	N, %
Melena	139 (21.5)
Hematemesis	66 (10.2)
Epigastric pain	452 (69.9)
Nausea	308 (47.6)
Vomiting	265 (41.0)
Dysphagia	77 (11.9)
Asthenia	348 (53.8)
Weight loss	501 (77.4)
Anorexia	125 (19.3)
Palpable epigastric tumor	57 (8.8)
Early satiety	180 (27.8)
Bloating	166 (25.7)

relationship ($p < 0.01$). Conversely, patients that experienced nausea, epigastric pain, palpable epigastric tumor mass or anorexia had a larger patient delay, but still with a highly significant statistical relationship between the symptoms and the patient delay interval ($p < 0.01$) (Fig. 3). The relationship between patient delay and other symptoms such as weight loss, bloating, early satiety, dysphagia did not have statistical significance.

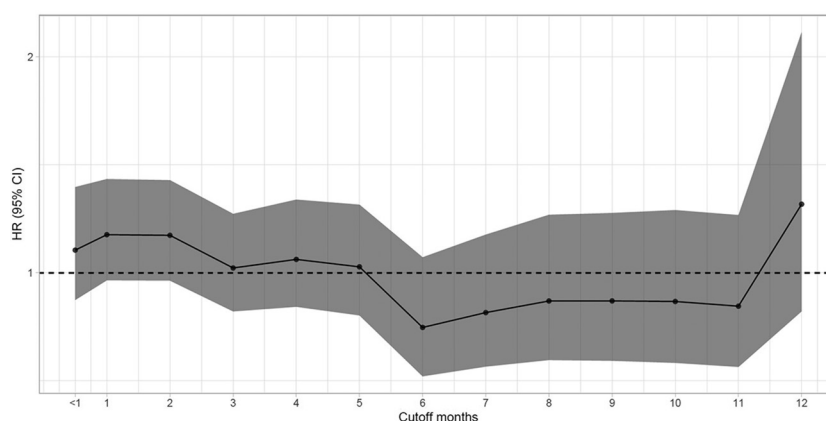
We have correlated the tumor characteristics with the patient delay and diagnosis delay interval. Regarding the localization of the tumor, no significant correlation was observed with patient delay ($p = 0.408$) and diagnosis delay ($p = 0.759$). The final histopathological stage of the tumor was not correlated with patient delay ($p = 0.210$), but a tendency for significance was identified with diagnosis delay ($p = 0.095$); the higher diagnosis delay was related to a higher staging. The grade of differentiation of the tumor had no statistically significant relationship with patient delay ($p = 0.726$) or diagnosis delay ($p = 0.394$).

DISCUSSION

Medical literature is scarce regarding the influence of the delay from the debut of the symptoms to the initiation of

($p = 0.199$). In women, a later presentation was observed ($p = 0.042$). No statistically significant relationship was identified between diagnosis delay and the sex ($p = 0.520$), age ($p = 0.627$) or area of origin ($p = 0.143$).

Patients that experienced melena or hematemesis had a shorter patient delay, with a highly significant statistical

**Fig. 1.** The effect of patient delay on overall survival at different cutoffs.

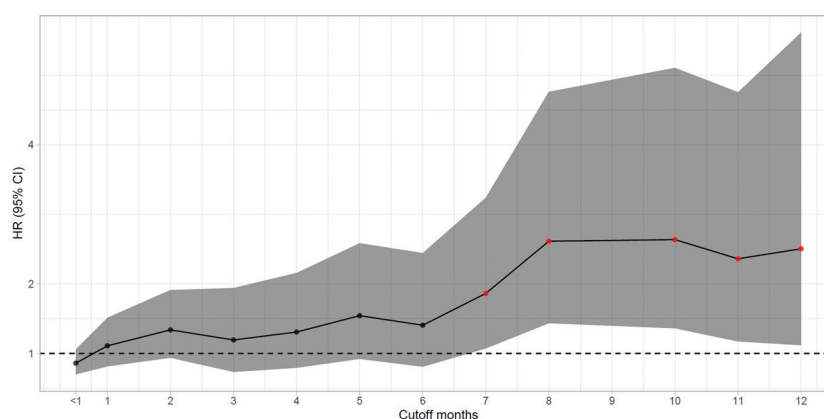


Fig. 2. The effect of diagnosis delay on overall survival at different cutoffs.

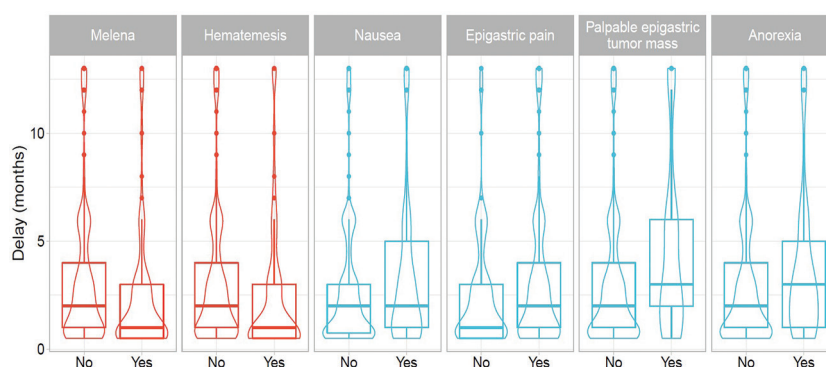


Fig. 3. Variables presenting a significant impact on patient delay.

gastric cancer treatment on survival. Several intervals have been proposed. The various definitions used in different articles makes the interpretation of the collective results very difficult. However, we need to acknowledge the importance of the subject; determining its relevance might offer not only details on the evolution of gastric cancer in time, but it can also underline the most important actions that healthcare professionals, especially in primary healthcare, need to take to minimize these delays. One of the most important studies [4] in the field describes three main intervals: patient delay, doctor delay and system delay. The first interval, “patient delay” refers to the time from the first symptom to the first contact with a general practitioner. The last two intervals comprise the time from the contact with the general practitioner to the initiations of the treatment, that overlies with the delays in both primary healthcare and secondary healthcare. Walter et al. [5] classifies the delay in four stages: appraisal, the time from the detection of the bodily change to the perception of a reason to consult a doctor, help-seeking, until the first consultation with a healthcare professional, diagnosis, the time from the first consultation to a diagnosis and pre-treatment, the interval from the diagnosis to the start of the treatment. Even though the definitions differ, all these studies have the common goal of assessing the influence of the delay on the evolution of cancer patients. For a better systematization, we have synthesized these definitions in Fig. 4; we can observe that different definitions overlap. Since there is no definitive conclusion on the subject [2], especially in gastric cancer patients, we believe that the

analysis performed in our study is a welcome addition for medical practice.

We used in our study two different intervals. Patient delay was defined as the time from the manifestation of the first symptom to the time of the first doctor consultation; this interval corresponds with the patient delay interval described by Olesen et al. [4], and it corresponds to the appraisal and help-seeking intervals together, described by Walter et al [5]. The diagnosis delay was described as the interval between the first medical consultation and the establishment of a diagnosis; this corresponds to the doctor delay and part of the system delay described by Olesen et al. [4], and it is a superposition with the diagnosis interval described by Walter et al [5]. We did not have enough data to assess the interval from diagnosis to treatment, in our study population. While the defined terms for delays differ between studies, they all underline the same important notions and their influence on the patient's evolution. Also, since there is a superposition of some of the terms, it allows us a fair discussion and pertinent conclusions.

The overall survival rate at 5 years was 46% for patients operated with curative intervention and 7% for patients with palliative care; these rates are similar to the ones reported in medical literature [10–12]. Even though recent advances in treatment have improved the survival rate of gastric cancer patients, the long-term prognosis remains poor; furthermore, this encourages the conduction of research in this field, to identify the modifiable factors that influence survival in gastric cancer patients.

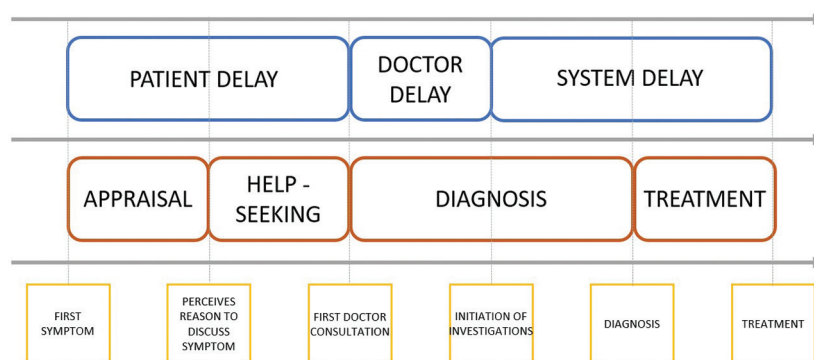


Fig. 4. Systematization of delay intervals.

Screening of high-risk populations has been proved to increase the diag diagnosis of early-gastric cancer and to improve long-term survival [13, 14]. However, in European countries, there is no designated screening program for gastric cancer [15, 16]. Therefore, diagnosing early gastric cancer, in the asymptomatic period, is the exception and not the rule [17–19]. Therefore, we intended to analyze if an earlier presentation would assure a better prognosis. We did not find a statistically significant relationship between patient delay and diagnosis delay intervals and overall survival; this conclusion is supported by other published studies [20–22].

From the time the first symptom occurs, there are various personal and environmental factors that might influence the decision to book a doctor's appointment [23–26]. Maybe one of the most important factors is the patient's worry about the experienced symptoms. This is illustrated in our study, by showing that certain symptoms have a higher impact on the patient's perception and therefore, determine an earlier appointment at a health-care professional. We observed that upper gastro-intestinal bleeding symptoms (either melena or hematemesis), epigastric pain, palpable epigastric tumor, nausea, and anorexia raised more concern than other clinical signs and symptoms, such as weight loss, bloating, early satiety or even dysphagia. This is reflected in the earlier presentation in the case of the first presented symptoms. One study analyzed the impact of the worry of the patient, as well as the general practitioner's worry in the referral to further investigations [27]. Therefore, along with the experienced symptoms, the concern that the patients and their doctors exhibit, plays an important role; misalignment in opinions increased the likelihood of having a prolonged delay.

Since several factors might influence the decision of a patient to solicit a consultation with a healthcare professional, we tried to see if there is a correlation between the characteristics of the patient and the delay in presentation or diagnosis. No statistically relevant correlations were identified. However, a trend for a later presentation at a healthcare professional was observed in female patients, but without statistical significance. Hansen et al. [28] reports several socioeconomic predictors of delay, but as shown above, this was not confirmed by our study.

Some studies discussed the influence of the primary healthcare professional's characteristics on the delay in diagnosis or treatment of gastric cancer patients [29, 30]. Even

though our study has not analyzed these factors, and they were not the focus of our present research, these potential implications should be kept in mind and analyzed in further research.

The characteristics of the tumor might determine an earlier presentation or an expedited diagnosis. We have analyzed tumor location, stage, grade of differentiation and histological subtype; no clear relationship was identified with either patient delay or diagnosis delay. Martin et al [31]. also analyzed the relationship between the delay in diagnosis and tumor location or stage, without finding statistical relevance.

The type of admission to hospital might be related to the overall survival of gastric cancer patients. Patients who were admitted through the emergency department had a worse overall survival, which might show the severity of the experienced symptoms that determined the patient to be considered an emergency. Also, patients admitted by transfer had also a poor prognosis; since our hospital is a tertiary care center, patients with severe illness are transferred to our department for specialized care, which might be the cause for the poor survival in this category of patients.

The findings of our study are consistent with the current information in the medical literature, and our report is one of the few studies that acknowledges that the debut symptoms are one of the only factors that influence the patient delay interval.

The limitations of our study include its retrospective design, the limitations of the data included in our database, and the subjective assessment of the patient delay interval, that is based on the approximation offered by each patient. Unfortunately, not enough data were provided to analyze the influence of the interval from diagnosis to treatment. Another important limitation to acknowledge is the difficulty to interpret the data from our study in the current medical context, that is diverse and variable regarding the definitions of the terms used to describe delays. The strengths of our study are the considerable number of patients and the multitude of factors included in the analysis, that are welcomed in a yet incompletely explored field.

CONCLUSIONS

The delay in patients' presentation at a health-care professional and the delay in diagnosis did not significantly influence the overall survival. Some symptoms, such as upper

gastrointestinal bleeding, abdominal pain, palpable epigastric tumor, nausea, and anorexia assured an earlier presentation. The patient demographic characteristics, as well as the tumoral characteristics are not correlated with the patient delay and diagnosis delay.

Conflicts of interest: None to declare.

Authors' contribution: A.P. conceived and designed the study. A.N., C.P. and A.F. gathered the data. D.S. analyzed and interpreted the data. D.S. and A.P. drafted the manuscript. N.A. substantially revised the manuscript. All authors critically revised and approved the final version for publication and agreed to be accountable for all aspects of the work.

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