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EDITORIAL

Role of symptoms in diagnosis and outcome of gastric cancer

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Abstract

Gastric cancer is one of the most common cancers and the second most common cause of cancer deaths worldwide. Apart from Japan, where screening programmes have resulted in early diagnosis in asymptomatic patients, in most countries the diagnosis of gastric cancers is invariably made on account on dyspeptic and alarm symptoms, which may also be of prognostic significance when reported by the patient at diagnosis. However, their use as selection criteria for endoscopy seems to be inconsistent since alarm symptoms are not sufficiently sensitive to detect malignancies. In fact, the overall prevalence of these symptoms in dyspeptic patients is high, while the prevalence of gastro-intestinal cancer is very low. Moreover, symptoms of early stage cancer may be indistinguishable from those of benign dyspepsia, while the presence of alarm symptoms may imply an advanced and often inoperable disease. The features of dyspeptic and alarm symptoms may reflect the pathology of the tumour and be of prognostic value in suggesting site, stage and aggressiveness of cancer. Alarm symptoms in gastric cancer are independently related to survival and an increased number, as well as specific alarm symptoms, are closely correlated to the risk of death. Dysphagia, weight loss and a palpable abdominal mass appear to be major independent prognostic factors in gastric cancer, while gastro-intestinal bleeding, vomiting and also duration of symptoms, do not seem to have a relevant prognostic impact on survival in gastric cancer.

Key words: Gastric cancer; Symptoms; Diagnosis; Survival; Cancer stage; Alarm symptoms; Dyspepsia

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INTRODUCTION

Although the incidence of gastric cancer is decreasing in many countries, it remains one of the most common cancers and the second most common cause of cancer deaths worldwide[1]. Since the early stage of the disease is often asymptomatic, diagnosis is frequently made at an advanced stage of the disease, characterized by poor prognosis with a reported 5-year survival rate of less than 30% in most series.

Unlike Japan, where the screening programme resulted in a 5-year survival rate of 90%, in Western countries, despite the introduction of open-access gastroscopy, delays in diagnosis still seem to be common and virtually affect the stage of gastric cancer at diagnosis as well as outcome of patients. In fact, in Western countries, where a screening programme is not feasible[2], diagnosis of gastric cancer inevitably relies on symptoms reported by patients. Therefore, the increased awareness of symptoms on the part the patients, as well as correct interpretation of the symptoms and prompt referral for investigation, could reduce the diagnostic delay and, theoretically, improve survival.

To date, perception of symptoms and reasons for seeking, or not, consultation have been more extensively investigated in functional gastro-intestinal disorders than in organic diseases[3,4] and, in several studies, the interpretation and analysis of dyspeptic symptoms seemed to be focused more on reducing the endoscopic workload than on improving the detection of gastro-intestinal malignancy. Finally, the few studies that have analysed the influence of diagnostic delay, namely the symptom-to-diagnosis interval, on survival in gastric cancer have shown disappointing results.

The present review, while focusing attention on an analysis of the literature dealing with the symptoms in diagnosing and suggesting prognosis of gastric cancer, aims to elicit insights into some clinical (unexplored or forgotten) aspects of dyspeptic symptoms and gastric cancer.

IMPORTANCE OF SYMPTOMS IN DIAGNOSIS OF GASTRIC CANCER

Dyspeptic symptoms and also the alarm symptoms that

usually identify dyspeptic patients at higher risk of organic dyspepsia are common not only in patients consulting the general practitioner but also in the general population[5]. Gastro-oesophageal reflux disease, peptic ulcer disease, and functional dyspepsia represent the most frequent causes of dyspeptic symptoms. Only in a few cases are dyspeptic symptoms caused by gastro-oesophageal malignancy[6].

Upper gastro-intestinal endoscopy is usually performed to study patients with dyspeptic symptoms. Endoscopy is, however, expensive, troublesome to the patient, and, in more than 50% of endoscopic examinations, no organic cause can be found[7]. Therefore, non-invasive treatment strategies such as *H pylori* test-and-treat or empirical treatment with acid inhibitory drugs, i.e., proton pump inhibitors and H_2-antagonists, have been proposed and it has become evident that these strategies are at least as effective as upper gastro-intestinal endoscopy followed by targeted treatment[7-10].

However, the main concern, in the application of empirical treatments of dyspepsia are the possibility of missing gastric cancer or of delaying the time to diagnosis. An accurate selection of patients with a higher risk of gastro-oesophageal cancer, to be immediately submitted to endoscopy, is thus very important. Alarm symptoms such as weight loss, dysphagia, signs and symptoms of upper gastro-intestinal bleeding, anaemia, and persistent vomiting, are likely to be more frequently associated with upper gastro-intestinal malignancies, and most guidelines recommend immediate endoscopy in all patients presenting these symptoms[11-13].

The evidence supporting the use of alarm symptoms as selection criteria for endoscopy is, however, inconsistent since, on the one hand, alarm symptoms are not sufficiently sensitive to detect malignancies and, on the other, the overall prevalence of alarm symptoms, in a population of dyspeptic patients is high, while the prevalence of gastro-intestinal cancer is very low.

The studies, so far, reporting a high prevalence of alarm symptoms in gastro-intestinal malignancies are mainly retrospective and, according to these studies, up to 90% of patients with gastro-oesophageal malignancies present alarm symptoms at the time of endoscopy[14-16]. Large prospective cohort studies have achieved less significant results. For example, Meineche-Schmidt[17] showed that, in a large cohort of primary care patients with dyspeptic symptoms, the majority of patients who developed gastric/oesophageal cancer did not present with any alarm symptoms, while Lieberman[18], who studied a large database of endoscopy reports, showed that only 56% of patients with gastric/oesophageal cancer had alarm symptoms.

This discrepancy in results between the different studies may be explained by the fact that, in retrospective studies, patients may have had more advanced cancers which are less often asymptomatic[19] or that the retrospective analysis may have over-estimated the prevalence of alarm symptoms before endoscopy.

Due to the low prevalence of gastric and oesophageal cancer in the population, studies on larger series are needed. A recent investigation by Janssen, which appeared as an abstract[20], combined individual patient data from 7 prospective studies thus referring to more than 13 000 dyspeptic patients undergoing endoscopy. This investigation, which likely offers a more reliable picture of the problem, reported a prevalence of alarm symptoms of 30% (3927/13 377) and of 62% (103/165) in patients with gastro-intestinal cancer. This resulted in a sensitivity of 62.4%, a specificity of 70.5%, a positive predictive value of 2.6%, and a negative predictive value of 99.3% when the parameter "having any alarm symptom" was used to diagnose the presence of cancer. Interestingly, none of each individual alarm symptom was able to identify more than 30% of patients with gastric or oesophageal cancer. Moreover, the prevalence of alarm symptoms did not differ between young (< 50 years) and elderly (> 50 years) patients (11/19, 57.9% *vs* 92/146, 63%).

The role of each individual alarm symptom for predicting cancer in patients referred to a "rapid access upper gastro-intestinal cancer" service was evaluated by Kapoor[21]. In that study, involving, prospectively, 1785 patients referred for urgent endoscopy for suspected organic disease (which derived either from the occurrence of alarm symptoms or the presence of non-responsive, uncomplicated dyspepsia), occurrence of gastro-intestinal malignancies and benign organic disease was 3.8% and 12.8%, respectively. Dysphagia and weight loss were the only symptoms found to represent significant predictive factors for cancer [Odds Ratio (OR) 3.1 and 2.6, respectively]; age > 55 years was also a predictor of cancer (OR 9.5) but, uncomplicated dyspepsia, irrespective of age, was actually found to be a negative predictor of cancer (OR 0.1). From these data the authors developed a model in which, in dyspeptic patients, dysphagia and weight loss would represent criteria to perform endoscopy at any age, while age > 55 years would represent an indication for immediate endoscopy, only in the presence of an alarm symptom.

To improve the diagnosis of gastro-intestinal cancer, age is considered an important factor. There is a gradual increase in the risk of gastric and oesophageal cancer with age, but, unfortunately, a clear cut-off is difficult to define. Although, in the vast majority of the populations studied, almost 90% of patients with cancer are > 50 years, albeit the age distribution of upper gastro-intestinal cancer may vary; indeed, in Poland, Boldys[22] showed that, in a high-risk tertiary care population, as many as 24% of patients with gastric cancer were < 45 years.

Use of the age criteria to select dyspeptic patients to investigate with endoscopy is considered safe by most authors, provided the age cut-off has been determined using data from the local population[23-25]. Male sex is also significantly associated with gastro-intestinal cancer and, according to some authors; the age threshold for endoscopy should be lowered in males to decrease the risk of missing cancer, and could be safely increased in females without affecting outcomes[25].

Approximately 3%-4% of the population, in industrialized countries, consult their general practitioner with upper gastro-intestinal symptoms each year, of which over 10% will have alarm symptoms[26]. The symptoms of early stage cancer may be indistinguishable from those of benign dyspepsia, while the presence of established

alarm symptoms may imply advanced inoperable disease. This represents a dilemma in terms of defining criteria and priorities for investigating upper gastro-intestinal symptoms, particularly in healthcare systems where the potential demand for endoscopy may exceed the level of provision.

Current guidelines, based on the rising incidence of malignancy with age, suggest that patients with uncomplicated dyspepsia be investigated, only if older than a cut-off age[12,13], but the concern of missing cancer in young dyspeptics may be overcome only by investigating every patient with recent-onset dyspeptic symptoms regardless of age. The Canadian (CADET) study, which examined 1021 patients referred from primary care units, without alarm symptoms, identified only 2 cancers[27]. Other studies have demonstrated that the endoscopic yield of cancer, in simple dyspepsia, is low and only very few of the identified cancers are resectable[15,28].

We do not know whether the incidence of malignancy in patients with uncomplicated dyspepsia is different from that in the non-dyspeptic population; but we do know that early gastro-intestinal cancers are asymptomatic and are usually diagnosed by chance in patients undergoing endoscopy for dyspeptic symptoms secondary to benign or functional conditions. The impact of delaying the diagnosis of gastric cancer while giving a short course of empirical treatment is unknown, but, probably, a strategy of initial non-invasive management is unlikely to significantly affect the outcome, in the majority of young patients with benign dyspepsia provided the physician promptly arranges endoscopy where appropriate, i.e., in the event of lack of response to empirical therapy[29].

PROGNOSTIC RELEVANCE OF SYMPTOMS IN GASTRIC CANCER

The prognosis of gastric cancer has improved, in recent years, at least in Eastern countries where the 5-year survival rate is 50%-60%[30-32]. On the contrary, survival rates in Western series are still dismal, ranging between 8% and 26%[33-37]. One of the main reasons for this discrepancy is the efficacy of screening programmes in Japan, where the high incidence and awareness of the condition, and ready access to endoscopy have led to cancers usually being diagnosed in asymptomatic patients or in patients with minor dyspeptic symptoms[38]. In Europe and Western countries, where a screening programme is not feasible, the diagnosis of gastric cancers is invariably made on account of symptoms.

Indeed, the onset, duration and features of dyspeptic and alarm symptoms may suggest the diagnosis of gastric cancer, but they also reflect pathological features of the tumour and, therefore, have some prognostic value.

To date, the survival rates of gastric cancer, as well as the differences in survival rates observed between Eastern and Western case series, have been mainly attributed to the stage of the tumour, namely the depth of gastric wall invasion and status of lymph node and metastasis. Reports in the literature investigating the prognostic factors in gastric cancer, have focused mainly on the relevance of tumour-related features (such as, tumour node metastasis (TNM) classification, histological type, tumour appearance, site and size) or treatment-related factors (extent of gastric resection and lymphadenectomy and post-operative treatment) other than on patient-related clinical features.

However, since the eighties and more consistently in recent years, the prognostic role of symptoms, particularly alarm symptoms, in gastric cancer survival, has been investigated.

Symptoms and cancer stage

The alarm symptoms accompanying dyspeptic symptoms do not only have a diagnostic role in indicating the possible presence of gastric cancer, but when referred to, at diagnosis, in gastric cancer patients, may suggest the site, stage and aggressiveness of cancer and usually indicate poor prognosis.

In a retrospective study on a series of 92 young gastric cancer patients, we have evaluated the relationship of alarm symptoms, such as dysphagia, anorexia, weight loss, gastro-intestinal bleeding and vomiting with pathology (intestinal or diffuse) and site of cancer and stage, according to the TNM classification. Patients presenting with alarm symptoms were comparable to those with uncomplicated dyspepsia as far as concerns age, sex and pathology of gastric cancer, but more frequently showed a proximal site and more advanced TNM stage[19]. These findings have been confirmed by Stephens, who also showed that the number of alarm symptoms, at presentation, correlated with the stage of the tumour, in that patients with the greatest number of alarm symptoms presented with the most advanced disease[39] and by Bowrey, in a more recent study, in which approximately 50% of the patients with alarm symptoms had stage Ⅳ disease[40].

Indeed, the relationship between symptoms and stage of cancer is conceivable if we consider the profile of symptoms in early gastric cancer which are not unlike those of benign gastric ulcer rather than advanced cancer. Epigastric pain and dyspepsia are very frequently present, whilst alarm symptoms occur in only a minority of patients. For instance, weight loss occurs in less than 40% of patients, in early gastric cancer, while it is a common feature of advanced gastric cancer[41]. The reasons triggering benign or malignant symptoms in gastric cancer, and whether benign may convert to malignant symptoms over time, deserve further investigation.

Specific symptoms and outcome of gastric cancer

Since symptoms correlate well with cancer stage at diagnosis, they are likely also of prognostic value. Indeed, several studies have assessed the prognostic value of specific alarm symptoms in gastric cancer, demonstrating that these may be independently related to the survival of patients with gastric cancer and that, an increased number of alarm symptoms and specific symptoms are closely correlated to the risk of death. Studies that evaluated the impact of alarm symptoms on gastric cancer survival showed that the presence of at least one alarm symptom might reduce the 5-year survival rate by an average of 26%[19,39,40]. We have also shown that the

risk of death is nearly threefold in patients with at least one alarm symptom compared with that in patients with uncomplicated dyspepsia[19]. Moreover, Stephens and Bowrey reported that the median survival for patients with alarm symptoms, from presentation to death, ranged from 7 to 11 mo *vs* 24 to 39 mo for patients without alarm symptoms[39,40].

These dismal prognostic data in gastric cancer patients with alarm symptoms are not completely new. Earlier studies and recent confirmation have shown that any symptom may have a significant and independent prognostic role in gastric cancer patients and that specific symptoms may have a particularly greater prognostic impact.

It is difficult to analyse, compare and describe the prognostic role of each alarm symptom reported in the literature on account of the different definition criteria of symptoms, retrospective collection of data in most studies, geographic and time differences in treatment-related prognostic factors, and different age of patients enrolled in the studies. However, of the alarm symptoms most widely considered, namely dysphagia, weight loss, palpable abdominal mass, gastro-intestinal bleeding, anaemia, persistent and continuous vomiting, the data published so far have consistently identified dysphagia, weight loss and palpable abdominal mass as the most relevant and independent prognostic factors in gastric cancer.

Weight loss has been considered among the potential prognostic factors for gastric cancer by at least 13 studies so far, and in 10 of these it resulted significantly and independently related to the fatal outcome[19,39,40,42-51]. It is not possible to calculate life expectancy in gastric cancer patients presenting with weight loss. However, the 5-year survival rate ranged from 13.5% to 31%[39,44] and the mean survival reported was less than 1.2 years[46,40]. Indeed, the prognostic relevance of this symptom is well known. It correlates with malnutrition and impaired immune response. Weight loss does not merely increase post-operative complications, but also reduces the response and increases the toxicity to chemotherapy[45,48,52]. Indeed, it has been shown that 10 d of pre-operative total parenteral nutrition (TPN), which is continued post-operatively, reduces the complication rate and prevents mortality in severely malnourished patients with gastro-intestinal cancer[53].

As far as concerns dysphagia, 5 studies evaluated the prognostic relevance of this symptom in gastric cancer, all of which showed that is was significantly associated with poor outcome[19,39,40,44,46]. Indeed, the prognosis of patients presenting this symptom seems to be even worst than that reported for weight loss, with a 5-year survival rate of 6%-7%[39,44], a mean survival < 10 mo[40,46] and risk of death > 7 times compared to that of patients without alarm symptoms[19]. Dysphagia usually identifies tumours of the cardia and proximal part of the stomach with prognosis being worse than in other locations for gastric cancer. Moreover, it is usually associated also with malnutrition and weight loss.

Another alarm symptom which is invariably associated with poor prognosis is the presence of a palpable abdominal mass. Eight studies have assessed the prognostic value of this sing[39,40,44-47,54] and all but one found a strong association with a very low 5-year survival rate (0%-20%)[39,44,54] and also with a very short life span (< 4 mo)[40,46].

The prognostic role of vomiting and gastro-intestinal bleeding is more controversial. As far as concerns vomiting, as an alarm symptom, 2 out of 4 studies[19,39,40,46] evaluated the prognostic significance of this symptom and showed that is was correlated with brief survival, namely a median survival of 9 mo, in one study[40], and a 5-year survival of 14%, in the other[39]. Indeed, this symptom implies a certain degree of subjective interpretation and it may be difficult to retrospectively consider it as an alarm symptom, if persistent and continuing, or as a 'simple' dyspeptic symptom if occasional or of mild degree.

Gastro-intestinal bleeding has been regarded as a prognostic symptom in 4 studies[19,39,44,47] but in none showed any significant impact on outcome, probably because haemorrhage may appear even in earlier phases of the tumour and may not necessarily be related to the stage. In none of the studies investigating the role of specific dyspeptic symptoms, such as epigastric pain or abdominal discomfort, were these significantly related to survival.

Duration of symptoms and outcome of gastric cancer

The stage of gastric cancer, at diagnosis, has been regarded as the most important prognostic factor for survival. We have shown that it is correlated with the presence of specific symptoms. It has been argued that prolonged duration of symptoms, or - in other words - delay in diagnosis, could result in missing a gastric cancer at a hypothetically curable stage and, therefore, with a negative effect on survival[55].

For this reason, several studies have assessed the impact of dyspeptic versus alarm symptoms on diagnostic delay, and of symptoms-to-diagnosis time interval on survival in gastric cancer. All studies showed, as expected, that delay in diagnosis was longer for patients without alarm symptoms compared to that of patients with alarm symptoms[19,39,40]. However, all these studies also showed that, despite the diagnostic delay, survival rate of patients with gastric cancer who lacked alarm symptoms, at the time of diagnosis, was better than that in patients with alarm symptoms at presentation. Paradoxically and more important, patients with uncomplicated dyspepsia with a delay more than 6 mo showed better survival rates[19,39,55-59].

Indeed, the duration of symptoms has been considered as a relevant prognostic factor in several studies. At least 14 studies have evaluated this prognostic aspect but all showed that duration of symptoms was not related to poor outcome[19,32,43-46,60-67]. It would have seemed obvious that the sooner a patient is treated for cancer, the better the prognosis will be. On the contrary, almost all studies published, so far, have shown that delay in diagnosis is not a relevant prognostic factor and more than one study demonstrated that long duration of symptoms is associated with the earlier the tumours are diagnosed, longer the survival[19,46,59,60].

Other studies have shown that gastric cancer patients with alarm symptoms have a poor prognosis despite a much shorter symptom-to-diagnosis time interval

compared to patients without alarm symptoms, providing indirect evidence that the relationship between duration of symptoms and prognosis is less important than the characteristics of the symptoms at presentation.

One possible explanation for this is that mild or dyspeptic symptoms, that do not alarm the patient or his/her doctor, might be associated with a cancer disease presenting a less aggressive behaviour and slower progress[68]. But this remains to be demonstrated, to date. Another possible explanation is that the delay in diagnosis in patients without alarm symptoms may, instead, be due to the long duration of dyspeptic symptoms, the onset of which had not been related to gastric cancer. In this case, less symptomatic patients tend to have a less severe/advanced disease.

However, it is noteworthy that this inverse relationship between delay in diagnosis and survival has been consistently observed in several studies in various parts of the world. The potential practical implication for this is that a diagnostic delay of 6 mo since presentation of symptoms could be an acceptable time to evaluate the outcome of treatment in patients presenting with uninvestigated, uncomplicated, dyspepsia, without affecting survival if gastric cancer is already present. This has also been demonstrated already in two clinical studies in which anti-secretory drug treatment delayed the diagnosis of upper gastro-intestinal adenocarcinoma without affecting outcome, in most patients[29], and by another where the outcome of patients in whom the cancer was missed, at a previous gastroscopy, showed a similar outcome to that of patients with prompt correct diagnosis[69].

However, it cannot be excluded that improving the diagnosis of gastric cancer, when it presents without alarm or severe symptoms, may result in better prognosis[70]. To date, in fact, the behaviour of symptoms, in gastric cancer, is still poorly understood. Gastric cancer patients with alarm symptoms, at diagnosis, may have complained of uncomplicated dyspepsia at the onset of their symptoms, and developed alarm symptoms later. We do not know whether these patients differ from those presenting with alarm symptoms, as far as concerns delay of diagnosis, features and stage of gastric cancer. Further prospective studies are, therefore, needed not only to evaluate this aspect but would undoubtedly contribute to reaching a more accurate evaluation of symptoms and their impact on prognosis. Symptoms may vary from the onset to the diagnosis and referral of symptoms may depend on social and cultural factors[71]. A supportive study, in this direction carried out by Meineche-Schmidt and Jørgensen[17] in a primary care setting revealed that the majority of patients in whom upper gastro-intestinal cancer developed did not have alarm symptoms at their initial primary care consultation. It thus follows that the diagnosis of upper gastro-intestinal cancer, in most patients, is delayed until alarm symptoms occur, with inevitable consequences in terms of prognosis.

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