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Original Articles

The Symptom-to-Treatment Delay and Stage at the Time of Treatment in Cancer of Esophagus

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Objective: The main purpose of this investigation was to measure the delay from the first symptom to treatment in esophageal cancer and to analyse the relation between the delay and stage at the time of treatment.
Methods: A total of 80 patients who were consecutively found to have esophageal cancer between 1 January 2007 and 30 July 2007 at Qilu Hospital of Shandong University in Jinan (China) were included in the retrospective study. Two groups of patients were compared, one group with good prognosis (patients in Stages I and II) and the other group with poor prognosis (patients in Stages III and IV). The symptom-to-treatment delay between the two patient groups was compared using the Mann–Whitney *U*-test.
Results: The median symptom-to-treatment delay was 2.1 months (range from 0.5 to 24). The total symptom-to-treatment delay was made up with the following components: (i) delay from the first symptoms to first contacting the health-care system (69%); (ii) delay from first contacting the health-care system to histological diagnosis of esophageal cancer (20%); and (iii) delay from histological diagnosis to end point (11%). A significantly shorter median symptom-to-treatment delay was found for patients with Stages I and II compared with III and IV ($P = 0.0177$).
Conclusions: Long delays still occur in patients with esophageal cancer. A few months delay before final treatment of esophageal cancer may have an impact on the stage of the cancer, and thereby on the patients' prognosis. Shorting the delay may result in early detection of esophageal cancer.

Key words: esophageal cancer – delay – diagnosis – stage – prognosis

INTRODUCTION

Esophageal cancer is the eighth most common cancer and the sixth leading cause of cancer death in the world. It was responsible for 462 000 new cases (4.2% of the total) and 386 000 deaths (5.7% of the total) in 2002. Esophageal cancer has a remarkable geographic variation in incidence (1). Approximately, a 20-fold variation is observed between high-risk China and low-risk western Africa (2).

Esophageal cancer is one of the most virulent tumors with a dismal prognosis. Not more than 14% of the patients could survive longer than 5 years despite the recent advances in surgical techniques (3). The underlying reasons for this disappointing low-survival rate are multifold: (i) ineffective screening tools and guidelines; (ii) over 50% of patients with advanced disease at diagnosis; (iii) high risk for recurrent disease after treatment; and (iv) limited survival achieved with palliative chemotherapy alone for patients with metastatic or unresectable disease. Clearly, additional strategies are needed to detect esophageal cancer earlier and to improve our systemic treatment options (4).

The outcome of esophageal cancer is correlated well with the stages according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system (5). When operated on in Stage I, the 5-year survival rate is 50–80%. The corresponding 5-year survival rate concerning Stages II and III is approximately 30–40% and 10–15%, respectively (6). Patient with metastatic (Stage IV)

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disease treated with palliative therapy have a median survival of <1 year (7). So, if recognized and treated on in Stages I or II, a considerable part of the esophageal cancer patients might thus be cured.

The main purpose of this study has been: (i) to investigate the delay from the first symptom-to-treatment of esophageal cancer; and (ii) to investigate the possible correlation between symptom-to-treatment delay and the stage at the time of treatment.

PATIENTS AND METHODS

During the period from 1 January to 30 July 2007, all the patients diagnosed as having esophageal cancer at Qilu Hospital of Shandong University, in Jinan (China) were studied, retrospectively. Patients with sarcoma, lymphoma, melanoma and carcinoma *in situ* of esophagus and cancers arising from gastroesophageal junction were excluded.

One of the authors interviewed each patient at their first visit to our hospital. Dates were recorded according to the patients' recollection, written information contained in the doctors' records during the diagnosis process, and the patients' hospital files. Details of the patients' first symptoms and the course of diagnosis and treatment were recorded.

The delays in diagnosis and treatment were measured from the date when the patient first experienced the symptoms that led to diagnosis. The end point was the date when the patient had definitive surgery or other cancer-specific treatment. The overall delay in months was recorded from the appearance of the first symptoms to end point for each patient and was divided into three periods: (i) time from appearance of the first symptoms to first contacting the health-care system; (ii) time from first contacting the health-care system to histological diagnosis of esophageal cancer; and (iii) time from histological diagnosis to the end point. Patients without complaints were considered to have no delay from the appearance of first symptoms to first contacting the health-care system.

The anatomical subsites of cancer lesions were determined according to the principal location where the tumor occurred, with distances measured from the mid-incisors using endoscopy as follows: (i) the cervical, from the cricoid cartilage (15 cm) to the suprasternal notch (18 cm); (ii) the upper thoracic, from 18 cm to carina (24 cm); (iii) mid-thoracic, from 24 cm to the middle between the tracheal bifurcation and gastroesophageal junction (32 cm); and (iv) lower thoracic, from 32 cm to the gastroesophageal junction (40 cm).

The tumors were staged according to the AJCC TNM staging system, whenever possible from operative specimens (5). For inoperable patients, esophageal cancer was staged according to the method of Moss et al. (8) by computer tomography.

The Mann–Whitney *U*-test was used to compare the patients in Stages I and II, as one group, with the patients in Stages III and IV, as the other group. The patients were grouped as such because of the fact that resected patients in Stages I and II have a good prognosis compared with the patients in higher stages. The Kruskal–Wallis test (9) was also employed to analyse the relation of delays with anatomical subsites or histology such as histological types and histopathological differentiations, if necessary.

The significance level was established at 0.05, and the *P* value is two-tailed. Statistical software used was the SPSS Version 11.5.

RESULTS

Patients' Characteristics

Eighty patients (61 men and 19 women) were included in this study. The median age of the patients when they first developed symptoms was 60 years (range 42–85 years).

The first symptoms or signs were dysphagia in 57 (71%) patients, abdominal or chest pain in 25 (31%), abdominal discomfort in two (3%), dyspepsia in five (6%), and hematemesis in one (1%). All patients have more or less symptoms, and some experienced more than one symptom.

All patients had endoscopy, barium swallow, and staging investigations (chest X-ray film, abdominal ultrasonography, and thoracoabdominal-computed tomography).

Tumor locations were cervical in two patients, upper thoracic in 10 patients, mid-thoracic in 42 patients, and lower thoracic in 26 patients. For histological types, 71 (89%) patients had squamous cell carcinoma, six (7.5%) had adenocarcinoma, two (2.5%) had undifferentiated carcinoma, and one (1%) had carcinoid. The histopathological differentiations of squamous cell carcinoma were poor in 21 cases, moderate in 41 cases, and well in nine cases. The differentiations of adenocarcinoma were poor in three cases and moderate in three cases. The differentiation of the patient who had more than one histopathological differentiation in the same mass was considered to be the poorer one.

The patients operated on in the study were, in addition, staged by histological examination of the resected materials. Ten (12.5%) had Stage I disease, 34 (42.5%) had Stage II disease, 31 (39%) had Stage III disease, and five (6%) had Stage IV disease.

Out of the total number of 80 patients, six (7.5%) were considered inoperable based on the results of the preoperative examinations. Concerning the distribution of inoperable patients, there were two out of a total of 34 in Stage II, three out of 31 in Stage III, and one out of five in Stage IV. The only inoperable patient in Stage IV received chemotherapy and others received radiotherapy as the initial cancer-specific treatment. The six patients were treated immediately when clinical stages were determined. Of the surgical procedures, 66 (89%) were regarded as potentially curative resections, eight (11%) were palliative resections. Concerning the distribution of palliative operation patients, there were four out of a total 31 in Stage III and four out of 5 in Stage IV.

Table 1. Breakdown of the symptom-to-treatment delay

Delays	Median[a] (range)	Mean[a]	Percent[b]
Delay from the first symptom to treatment	2.1 (0.5–24)	2.9	100
First symptoms to first contacting health-care system	1.2 (0.2–21)	2.0	69
First contacting to histological diagnosis	0.25 (0–6)	0.6	20
Histological diagnosis to cancer-specific treatment	0.25 (0–1.1)	0.3	11

[a]In months.
[b]Percentage of the symptom-to-treatment delay.

The Symptom-to-treatment Delay and Its Impact on Stage

The median delay concerning the interval from the appearance of the first symptoms to end point was 2.1 months. Twenty-nine percent had a delay of more than 3 months, 19% more than 4 months, and 11% more than 6 months. Table 1 shows the breakdown of this delay. Delay from the appearance of the first symptoms to first contacting health-care system accounted for 69% of the total, delay from first contacting health-care system to histological diagnosis (20%), and delay from histological diagnosis to treatment (11%). Fifty percent of patients had a delay more than a month from the appearance of the first symptoms to first contacting the health-care system, 21% more than 2 months, and 7.5% more than 4 months. Thirty percent of patients were histologically diagnosed when first contacting the health–care system. Approximately 21% of patients had histological diagnosis more than a month after first contacting the health-care system and 5% more than 3 months. Sixty-four percent of patients received operation or other cancer-specific treatments in a week after histological diagnosis and 5% have a delay more than 2 weeks from histological diagnosis to initiation of cancer-specific treatment.

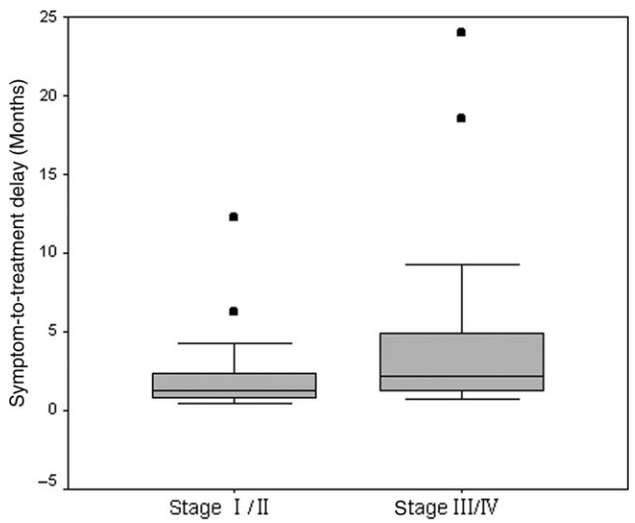

Figure 1. Box plot for the symptom-to-treatment delay in relation to stage of esophageal cancer (thick line = median, box = interquartile range, whiskers = 95% range. The 'filled circle' represents the 5% cases that lie out of the whiskers) 127 × 101 mm (96 × 96 DPI).

The relationship between stage of esophageal cancer and symptom-to-treatment delay is shown in the box-plots in Fig. 1. The median delay of first symptom-to-treatment is 1.8 months for Stages I and II and 2.2 months for Stages III and IV, and the difference is significant between the two groups ($P = 0.0177$).

The relationship of symptom-to-treatment delay or delay from the appearance of first symptoms to first contacting the health-care system with anatomical subsites, histological types or histopathological differentiations was also analysed as shown in Table 2. No significant difference was found in the comparison of delays in patients with different anatomical subsites, histological types or histopathological differentiations ($P > 0.05$).

DISCUSSION

Although esophageal cancer is a relative common disease in China, the results of this study indicate that long delays still exist in diagnosis and treatment of the disease. We have found that the median overall delay from the appearance of first symptom-to-treatment was 2.1 months. A quarter of patients had 3 months of overall delay and 11% of patients had 6 months. Delay from the appearance of the first symptoms to first contacting health-care system accounted for 69% of the total, delay from first contacting health-care system to histological diagnosis was 20%, and delay from histological diagnosis to treatment was 11%.

Table 2. Relation of delays with anatomy and histology

Tumor characteristics	Median STD[a]	*P*	Median SCD[b]	*P*
Anatomical subsites[e]				
Upper third[c]	2.6		1.5	
Mid-thoracic	2.2	0.750	1.5	0.567
Lower thoracic	2.1		1.0	
Differentiations of SCC[d,e]				
Well	2.3		1.0	
Moderate	2.1	0.881	1.0	0.974
Poor	2.1		1.5	
Histological types[f]				
SCC[d]	2.1		1.0	
Adenocarcinoma	2.2	0.669	1.6	0.738

[a]Symptom-to-treatment delay (in months).
[b]Symptom-to-first-contacting delay (in months).
[c]Including both cervical and upper thoracic.
[d]Squamous cell carcinoma.
[e]Compared by Kruskal–Wallis test.
[f]Compared by Mann–Whitney *U*-test.

The measurement of delay times presents a number of problems. The difficulty of obtaining reliable information is one such problem, since the responses provided by patients cannot be validated against a gold standard (10,11). Most former studies have only relied on the memory of patients or on hospital records. But in this study, except for the two data resources, others have been based on retrospective analysis of the written information contained in the doctors' records for those patients, who are subsequently identified as suffering from cancer. A major advantage of this method is its relative objectivity, since the information is based on firm written evidence as much as possible.

The median overall delay, similar to the median overall delay (2.2 months) found by Wittzig et al. (12) in Germany, in our study is shorter than that in former studies. Jones and Dudgeon (13) have found 3 months of median delay from first contacting the health-care system to treatment. Martin et al. (14) have found more than 4 months of median delay from the first symptoms to histological diagnosis of the disease. Both studies were conducted in Britain. Median delay from first symptoms to first contacting the health-care system in our study is longer than that in the study by Martin et al. (0.5 months), while delays after contacting the health-care system are shorter than the both studies. The reasons for the difference are multifold. And the difference in the health-care system is one of them. In China, medical insurance covers only a quarter of the whole population. Large comprehensive hospitals play a main role in health care of the people, and the community health-care system is undeveloped. Most of the patients go to large hospitals directly when they think their disease is severe. While this is different in Britain who has the full-population medical insurance and developed community health-care system, and all the patients treated by specials must be referred by general practitioners in community clinics. So the British patients, who have shorter delay from the first symptoms to first contacting the health-care system for medical services, are easier to access in Britain, but have to wait longer for the reference of the general practitioners and making appointment with the specials.

Moreover, we has also found significantly a shorter median overall delay for patients with Stages I and II compared with Stages III and IV ($P = 0.0177$) in this study. This may indicated that a few months delay in diagnosis and treatment has a significant influence on the stage of the esophageal cancer, and therefore, for the prognosis of the disease.

Studies calculating the growth of clinical tumors based on mathematical models suggest that it takes more than 10 years from the appearance of the first cancer cell to the possibility of clinically detecting a tumor by conventional investigations. One may argue that once an esophageal cancer is clinically and/or radiologically manifest, there has been a long tumor history of a number of years, and it seems unlikely that the prognosis is changed by the relative short delay time in diagnosis and treatment. However, the median values of potential doubling time in esophageal tumors are 4–5 days with a range of 2–20 days among the fastest of all types of tumors (15). A few months delay may allow the tumor to double several times if not considering cell loss. And the growth of tumors is exponential, which means that even if the history is long, the growth at the time of discovery is more rapid. So, long delays probably are a negative factor for the patient's prognosis (16).

Many studies have been carried out into the impact that delay in cancer diagnosis and treatment may have on the stage of the tumor at the time of surgery or the diagnosis, as well as the impact of delay on survival. Different studies have indicated a relationship between delayed diagnosis and the stage of the cancer. Some authors have found that a shorter delay progressively decreases the degree of invasion and increases the survival rate (17–19). Others, however, have asserted that there is not necessarily any relationship between delay, the extent of invasion, and mortality (11,20–22), and some have even indicated that shorter delay associated with poor prognosis (23). The reason for contradiction of the studies is not clear. However, esophageal cancer may be different with the following characteristics: lying in the unique narrow digestive tract that enables the disease to be detected earlier; and the relative stable biological behavior that approximately 90% of pathological types are squamous cell carcinoma. Both the results of Martin's and our studies have suggested that longer delay before final treatment of esophageal cancer increase the stage of the cancer, and thereby worsen the patients' prognosis (14).

In the present study, we also analysed the relationship of symptom-to-treatment delay or delay from the appearance of first symptoms to first contacting the health-care system with anatomical subsites and histology concerning histological types and histopathological differentiations, in order to find if there any group of patients at one subsite or with a histological type or a histopathological differentiation having significantly shorter median overall delay or seeking for medical advices significantly faster. However, no such group of patients had been found in our study. And because of the small case number of other types, histological types were only compared between squamous cell carcinoma and adenocarcinoma, and histopathological differentiations were analysed among squamous cell cancers.

The symptom-to-treatment delay is a highly complex variable that reflects the behavior of the patient and the physician, tumor biology, the functioning of the health-care system, and sociocultural norms. The delay is very important because cancers grow continuously, albeit at differing rates. Reducing them should result in tumors being diagnosed at earlier stages. As regards the patient's delay, it may be the one delay that is most difficult to decrease. Two factors might diminish the time. The first is information to the general public about the symptoms and severity of this deadly disease. The other important factor is the access to primary health care: the easier this is, the more patients will seek attendance for their symptoms.

The doctors' delays account for approximately one-third of the total delay. Thirty percent of patients were histologically diagnosed when first contacting the health-care system and 64% of patients received operation or other cancer-specific treatments in a week after histological diagnosis in our study. The doctors' delays are shorter than that in former studies as discussed previously, but more radical use of endoscopy and speeding up hospital assessment may decrease the delays further.

In conclusion, we have shown that there is a median delay of 2.1 months from the appearance of first symptoms to end point in patients with esophageal cancer. We believe that this is clinically important because the delay is associated with worsening tumor stage and poorer prognosis. But the present study is retrospective and of relatively small size and have relied on the memory of patients or on hospital records. Bias cannot be completely avoided. Further prospective investigations with large size of patient number are needed. However, it gives an idea about the delays in the diagnosis and treatment of esophageal cancer and made us assess where we could be faster.

Conflict of interest statement

None declared.

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