


Synchronous peritoneal involvement can also be technically resectable. In this study, this was the case for 10%, half the number found in other series (28,29), and the survival probability was surprisingly high (50% at 5 years), a figure that is considerably higher than the 29% reached in another series (28). These data suggest that our series included a more favourable selection of cases. Despite limitations, we feel that this therapeutic option should be evaluated in strictly selected cases. While not routinely recommended, laparoscopic diagnosis may be useful in this selection process (30).

Finally, up to 10% of patients are found at diagnosis to have a tumor that has extended to one or more adjacent organs. When only one adjacent organ is involved, a potentially curative resection is considered viable (23), but if two or more organs are affected, there is little hope that resection will enhance chances of survival (31,32). This study has grouped together all other cases of exclusively affected organs aside from the liver and peritoneum. Here it is seen that surgery substantially enhances survival as well (Fig. 3c). This analysis has notable limitations, namely the grouping together of different organs and the retrospective nature of the study, which makes it difficult to extrapolate solutions that are applicable to particular situations. Nevertheless, it still suggests that resection is useful for carefully selected patients. Given that available information is still very limited, new studies are needed to clarify therapeutic options for each situation (33,34).

In conclusion, different metastatic sites show differentiated forms presentation characteristics, which suggests that they reflect the progression of tumors which are at least partially different in origin. When the primary tumor and its extension to one organ are detected at the same time, therapeutic options capable of significantly prolonging survival are feasible in selected cases. Broad-based prospective studies are needed to determine the benefits and limits of surgical possibilities.

REFERENCES


<table>
<thead>
<tr>
<th>Site of metastases (*)</th>
<th>RR</th>
<th>LOWER</th>
<th>UPPER</th>
<th>p</th>
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<tr>
<td>Peritoneum</td>
<td>1.37</td>
<td>0.95</td>
<td>1.97</td>
<td>0.09</td>
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<td>0.66</td>
<td>1.23</td>
<td>1.51</td>
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<td>Surgery (**)</td>
<td>1.53</td>
<td>1.00</td>
<td>2.35</td>
<td>0.05</td>
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<tr>
<td>Other/none</td>
<td>2.92</td>
<td>1.78</td>
<td>4.80</td>
<td>&lt;0.001</td>
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</table>

Table IV. Final model using Cox’s analysis of proportional hazards

Reference: (*) Only liver. (**) Curative surgery
Overall significance of model: < 0.001
HR = hazard ratio, CI 95% = 95% confidence interval
All this suggests that patients with synchronic disease should be considered candidates for surgery after an evaluation with very strict selection criteria. These should include factors such as the patient’s baseline situation (24), possibilities of surgical borders (24,26), and metastases size (9).

(24). All this suggests that patients with synchronic disease should be considered candidates for surgery after an evaluation with very strict selection criteria. These should include factors such as the patient’s baseline situation (24), possibilities of surgical borders (24,26), and metastases size (9).
Liver involvement, on the other hand, may be of two types: adjacent to the gastric tumor or distant. All this suggests that metastatic routes may be influenced by the nature of the primary tumor, and that the different metastatic sites represent progressive forms of processes at least partially different in origin, something that concurs with previous findings (20). This information could be useful in developing systems to predict the course of the disease in patients with a new diagnosis, as well as probability of recurrence and other organ involvement (3,21). All this would aid in planning follow-up and the need for co-adjunctive treatment (22).

This study, like others (23), points out that prognosis significantly worsens when the disease has spread to more than one site (Table IV). In recent years, the indication of hepatectomy for patients with liver metastases has become more widespread. Among those operated, 5-year survival reaches up to 34% (7), with a mean of 20% (24). Nonetheless, these figures may vary depending on the presentation forms of metastases. Whereas in patients with liver involvement adjacent to the primitive tumor 5-year survival may reach up to 66%, in those with non-adjacent metastases it may approach 0% (8). Another controversial aspect is the attitude to be held depending on the time of metastases presentation. While there is agreement regarding surgical possibilities for patients with metachronic liver involvement, the attitude to adopt in cases of synchronic presentation is in debate (7-9,25-27). Our study shows that in those cases with synchronic liver metastases in which curative surgery is possible, 5-year survival improves significantly and reaches 20%, these figures being similar to those in other series.
Table III lists the main characteristics of patients who presented with exclusive liver metastases, but prognosis improved significantly for them when compared with those who did not undergo surgery (Fig. 3a; \(p = 0.002\)). Among these 11 patients, 5 had liver involvement because of proximity, while 6 had distant metastases, and survival reached 5 years post-diagnosis in 1 and 2 cases, respectively. Resection was only possible in 7 out of 70 (10%) patients in whom the peritoneum was exclusively affected, but here again prognosis improved significantly with respect to those who did not undergo surgery (Fig. 3b; \(p = 0.001\)). Likewise, among patients with only another intraabdominal organ affected, an improved prognosis was seen in those on whom a complete resection of disease could be performed (25 out of 121; 20.7%) (Fig. 3c; \(p = 0.001\)).

The results of the best Cox model are presented in Table IV. No surgery (hazard ratio: 2.92), and simultaneous liver and peritoneum involvement (hazard ratio: 1.62) were the factors associated with a greater probability of death.

**DISCUSSION**

This study points out three clinically relevant aspects in patients with gastric cancer and metastases at diagnosis. The first is that the length of the symptomatic period is of little clinical relevance for evaluating the extension of the disease. The second is that metastases to one neighbouring organ or another does not occur randomly, but is instead related to different factors, including the characteristics of the primary tumor. Finally, although prognosis is generally poor, in selected cases with extension to only one organ, resection increases survival.

As a whole, a significantly lower number of surgical curative resections were performed on patients diagnosed in advanced stages of disease (Table II), and their prognosis was poorer (Fig. 1). Although one might think that these two facts are related to a longer diagnostic delay, our study revealed that actually the opposite is true: this delay is slightly shorter among patients with advanced disease. This data suggests that the length of the symptomatic period of the disease is of little clinical value (15,16), a circumstance already observed for tumors in other sites (17-19). Also relevant is the fact that the proportion of patients diagnosed with advanced disease has not diminished over the course of the years. This implies that technological improvements are of no use to facilitate diagnosis at earlier stages. Thus, new diagnostic strategies are needed if we wish to improve this situation.

Far from being a unique entity, advanced gastric cancer includes clinically different problems. This study shows that the two most frequent sites of metastases, the liver and peritoneum, have differentiated presentation characteristics. Patients with peritoneal involvement are older, suffer from larger tumors, more frequently belong to the massive type of gastric cancer, and the Lauren's...
MATERIAL AND METHODS

We made a retrospective cohort study that included all patients diagnosed with gastric adenocarcinoma at Xeral-Calde Hospital, Lugo, and Juan Canalejo Hospital, A Coruña, between January 1975 and December 1993. As the method of selection and definition of variables collected have been previously described (11), we will only discuss the most relevant aspects.

The date of diagnosis was considered to be the day when a histological diagnosis of gastric adenocarcinoma was made. The time elapsed between the onset of early symptoms and date of diagnosis is referred to as the “diagnostic delay”. Tumor localisation was established following a classification that divides the gastric chamber into three patients. Lauren’s classification was used for histological evaluation (12). The extent of the disease was determined according to the fourth TNM classification published in 1987 (13). Extra-gastric extension was considered to exist if either during the diagnostic process or subsequent surgery at least one of the following circumstances was seen: a) existence of adenocarcinoma in the biopsy of another organ in addition to the stomach; b) presence of adenocarcinoma cells in the ascitic or pleural fluid; c) surgical report referred to multiple organ involvement, and biopsy of at least one organ was obtained; and d) evidence of extension upon reviewing imaging studies from patients who did not undergo surgery.

It was considered that some type of surgery had been performed when surgical reports described any sort of intervention other than a mere inspection or a biopsy capable of altering the course of the disease in one way or another. Otherwise, the case was classified as “no surgery” or undergoing “minimally invasive surgery”. “Curative resection surgery” refers to a complete extirpation of both the original tumor and metastatic implants (when present), no post-surgical perception of visible tumor tissue (metastatic or lymph node involvement), and resection borders were also found to be disease-free.

In order to determine survival time, we evaluated multiple hospital and extra-hospital records, and contacted patients and families as well as family doctors when deemed necessary. Survivors were followed up until at least August 1, 1996. All patients and all deaths from any cause were included in our estimation of survival probability.

For the statistical analysis, the Chi-squared test was used to evaluate differences between two qualitative variables, and the Chi-squared tendency test was utilised when evaluating the course of the disease over different time periods. Student’s t test was used to compare two quantitative variables. Survival probability was estimated by the Kaplan-Meier method. The log-rank test was used to evaluate the existence of significant differences between groups. In determining prognostic factors, Cox’s models of proportional hazards were used. Variables included in the maximum model were: sex, age (stratified as: under 50, 50-64, 65-79, and 80 or above), period of diagnosis (1975-1987 or 1988-1993), population of place of residence (under or over 30,000 inhabitants), tumor location (upper, middle, or lower third, massive or gastric stump), surgical procedure (curative, palliative, or minimal surgery/no surgery), Lauren’s classification (intestinal, diffuse, or mixed type), and site of metastases (only liver, only peritoneum, liver and peritoneum, or another intraabdominal site). Hazard ratios were evaluated by graphic methods. We analysed the terms of interaction, but as they were not significant, these were not included in the final model. The differing hazards of dying 5 years after diagnosis were calculated with their 95% confidence intervals using the results of regression models. Data analysis was performed with the statistical program EGRET (14).

RESULTS

Within the designated time period, 2,334 patients were diagnosed of gastric cancer. Metastases to any site were detected at diagnosis in 585 (25.1%) patients. The liver (346 cases, 14.8%) and peritoneum (161 cases, 6.9%) were the most frequently involved sites (Table I). In the evaluation of the number of organs simultaneously affected in a patient, we found that metastases to only one organ was the most common scenario. Exclusive involvement liver was found in 213 (9.1%) cases (66 adjacent extension and 147 non-adjacent metastases), of the peritoneum in 70 (3.3%), and of other organs in 121 (5.2%). Simultaneous involvement of more than one organ was detected in 181 (7.8%) patients, with a liver-peritoneum association being most frequently found (40 patients, 1.7%).

Table II reflects the primary variables for all patients according to whether or not metastases were detected at the time of diagnosis. As a whole, patients with metastases had a slightly shorter diagnostic delay, a larger proportion of massive gastric involvement, and a lower percentage of curative resections. On the other hand, no differences were seen regarding age, sex, period of diagnosis, or histological type.

<table>
<thead>
<tr>
<th>Table I. Organs affected at diagnosis</th>
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<td><strong>Number</strong></td>
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<tr>
<td>Liver</td>
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<td>Peritoneum</td>
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<td>Pancreas</td>
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<td>Lung</td>
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<td>Ovary</td>
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<tr>
<td>Other</td>
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<td>No metastases</td>
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</table>
Advanced gastric cancer: characteristics at presentation and therapeutic possibilities

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ABSTRACT

Objective: to analyse the presentation forms and prognosis of patients with advanced gastric cancer at the time of diagnosis.

Design: retrospective cohort study.

Patients and methods: we studied all patients with gastric cancer (n = 2,334) and synchronic metastases diagnosed in Lugo and A Coruña hospitals between 1975 and 1993. We estimated survival probability using the Kaplan-Meier method, and prognostic factors with Cox’s regression models.

Results: metastases were detected at the time of diagnosis in 585 (25.1%) patients, with the liver (346; 14.8%) and peritoneum (61; 6.9%) being the most frequently involved sites. The liver was exclusively affected in 213 (9.1%) cases, the peritoneum in 70 (3.3%), and another intraabdominal site in 121 (5.2%). Patients with peritoneal metastases were older (p = 0.05), more commonly had a diffusely type of cancer according to Lauren’s tumor classification (p < 0.001), and underwent surgery more frequently (p = 0.01). Curative resection was possible for only 11 (5.2%), 7 (10%), and 25 (20.7%) patients with metastases in only the liver, peritoneum, or another site, respectively, but in all cases survival probability was significantly enhanced. No surgery (HR = 2.92), and simultaneous involvement of the liver and peritoneum (HR=1.62) were factors associated with a higher mortality rate.

Conclusions: patients with gastric cancer and metastases in only one intraabdominal organ show characteristic forms of presentation. Furthermore, in all cases candidacy for surgery should be carefully evaluated, as prognosis may improve in selected patients.

Key words: Gastric cancer. Liver metastases. Peritoneal metastases. Prognostic factors.

INTRODUCTION

The extension of the disease at the time of diagnosis is the most crucial prognostic factor of patients with gastric cancer (1). Peritoneal involvement, liver metastases, extensive spreading to the lymph nodes or extension to adjacent organs are the characteristic forms of presentation that the disease may take at advanced stages (2). Despite their common origin, clinically relevant differences exist among them. For example, peritoneal involvement is associated with clearly differentiated presentation forms, histological patterns and dissemination routes (1,3-6). However, there have been few studies focused on analysing these differing aspects, and among those that exist, findings are sometimes contradictory and have not been confirmed in different geographic settings (7-9). Furthermore, while prognosis is generally poor, the best therapeutic option for each site and time of presentation is still a matter of discussion.

In Spain, gastric cancer is the tenth leading cause of death (10), and up to 50% of patients are diagnosed in advanced stages of the disease (11). Despite the scope of this problem, the characteristics of these patients at presentation are poorly understood in our country, and broad-based series analysing therapeutic options and prognosis are also lacking.

For these reasons, the purpose of our study was factors to analyse the presentation characteristics and prognosis of patients with advanced gastric cancer at the time of diagnosis.