

Factors affecting prognosis after curative surgical treatment of gastric cancer

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ABSTRACT

Background: Gastric cancer is a cancer with a poor prognosis. Surgery with adequate lymph node dissection is the only potentially curative treatment for gastric cancer. The aim of this work is to determine the prognostic factors after curative resection for gastric cancer. **Patients and Methods:** We retrospectively assessed 66 patients who underwent operation for gastric cancer (excluding the eso gastric junction cancer) in a single institution between 2001 and 2015. **Results:** There were 25 women and 40 men. The median age was 60 years (21–87). Four patients died (6.1%). A total gastrectomy was performed in 35 cases, and a subtotal gastrectomy was performed in 30 cases. The type of lymphadenectomy was D2 lymphadenectomy in 35 cases and D2 without splénectomy in 30 cases. The pathologic review of the slides revealed that the tumors were stage T3–T4 in 49 cases. The median number of lymph node removed was 14. Median survival rate was 34 months. The median follow-up was 24 months. In multivariate analysis, the location in the fundus, lymph nodes involvement, and involvement of located organs were associated with poor prognosis. **Conclusion:** After R0 resection with DII lymphadenectomy, fundus location, lymph node Involvement, and involvement of organs were independent predictive factors for survival.

Key words: Gastric cancer, prognosis, recurrence, surgical resection

INTRODUCTION

Gastric adenocarcinoma is one of the most common cancers worldwide despite its declining overall incidence. Although the incidence is clearly decreasing, it is still considered one of the most causes of mortality related to cancer, due to its poor prognosis.^[1] Gastric cancer is a severe condition, mainly explained by its lymphatic, peritoneal, and metastatic spread. Surgery is the most therapeutic option that improves survival. Surgical technique is well defined, based on a large resection and lymph node dissection, which allows a radical R0 resection.^[2] Although the notable progress in surgical and postoperative care management, improving the early postoperative outlook, distant prognosis is still severe. Adjuvant chemotherapy

and/or radiotherapy are in principle necessary to increase the efficiency of surgical treatment. Therapeutic indications and strategy require a multidisciplinary agreement between surgeons, gastroenterologists, radiologists, pathologists, oncologists, and radiotherapists. The aim of this work is to determine the prognostic factors after curative resection for gastric cancer.

PATIENTS AND METHODS

We retrospectively assessed 65 patients, operated for a gastric adenocarcinoma, from January 1, 2000 to June 30, 2015, in the General Surgery Department of the Hospital of Bizerte, Tunisia.

Eligibility criteria

Patients operated for a gastric adenocarcinoma, of any location, during the study period.

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Exclusion criteria

Patients who were not operated for a metastatic or nonresectable cancer, the other histological types (lymphoma, neuroendocrine tumors, and stromal tumors...), tumors of adjacent organs invading the stomach and the adenocarcinoma of the cardia.

A subtotal gastrectomy with a gastrojejunal anastomosis was performed for the gastric antrum tumors. In all the other cases, patients underwent a total gastrectomy with an esophagojejunal anastomosis. Subtotal gastrectomy was associated to a D2 lymph node dissection, including the nine first lymph node according to the Japanese classification.^[3] The lymph node dissection is associated to a double omentectomy, with a resection of the omentum minus, and the gastrocolic omentum. The left gastric artery was ligated in its origin: a dissection of the celiac axis and of the hepatic artery was performed simultaneously. Total gastrectomy was associated to a D2 lymph node dissection, including the first and the second lymph node chains (from the first to the eleventh lymph nodes). In most cases, the lymph node dissection was not completed with a splenectomy; its considered as a D1, 5 dissections.

Evaluation criteria in the study were the overall survival, and factors conditioning the occurrence of recurrence and disease-free survival.

The data Excel and statistical software (SPSS for Windows, version 10.0, Chicago, IL). Results were expressed in the form of percentage and average values. The survivor ship curve was performed according to the Kaplan–Meier model. Comparison of the percentages was based on Chi-square test and the Fisher test. Comparison of the survivor rates curves was based on the log-rank test. Signification was fixed on 0.05 for all the statistical tests.

To identify the risk factors independently related to the event, a multivariate logistic regression analysis was carried out. Multivariate analysis allowed a precise odds-ratio calculation, measuring the proper role of every factor, and mainly identifying predictive factors of recurrence at factors affecting the survival

RESULTS

The median age in the study was 66 years old, range (31–82 years). There were 40 men (69.6%) and 25 women (30.4%). The sex-ratio was 2.28. Thirty-four patients had medical history (52.3%). Predisposing lesions were observed in eight patients such as Biermer's anemia in two cases, Menetrier disease in three cases, and gastric ulcer in three cases. Diagnosis average period defined by the delay from onset of symptoms to surgery was 6 months.

In peroperative exploration, lesions were in the gastric antrum in 30 cases (46.1%), the gastric body in 18 cases, the fundus in 14 cases, and the lesser curvature of the stomach in 3 cases. The tumor was locally advanced with the invasion of adjacent organs in 4 cases. Ascites was observed in one case and a local carcinosis in the diaphragm muscle in one case.

Surgical procedures were a subtotal gastrectomy in 30 cases (46.2%) and a total gastrectomy in 35 cases (53.8%). Multivisceral resection was performed in 6 cases, concerning the spleen in 3 cases, the diaphragm crus in one case, transverse colon in one case, and a hepatic resection in one case. A D1 lymph node dissection was performed in 5 cases; a D2 lymphadenectomy was performed in 60 cases. Resection was curative in all cases.

Concerning the histological features, the adenocarcinoma was well-differentiated in 15 cases (23%), moderately differentiated in 30 cases (46.1%), and undifferentiated in 20 cases (30.8%).

The average size of the tumor 3.6 cm ranges (1–8 cm). The tumor was classified T1–T2 in 16 cases and T3–T4 (advanced tumor) in 49 cases.

Average number of taken lymph nodes was 14, with extreme values of 4 and 36. Tumors were classified N0 in 27 cases, N1 in 36 cases, and N2 in 3 cases.

An early postoperative death was observed in 4 cases (6.5%). Postoperative recoveries were uneventful in 47 cases (72.3%) and complicated in 18 cases (27.7%). Medical complications happened in 6 cases (9.2%). Surgical complications occurred in 12 cases (18.4%). Surgical complications involved anastomotic fistula in 6 cases, duodenal fistula in 2 cases, and acute pancreatitis in 3 cases and postoperative hemorrhage in one case.

Overall, survival rate was 62% after 3 years [Figure 1]. The median survival was 24 months, with extreme values ranking from 5 to 62 months.

Based on an univariate analysis [Table 1], global survival was influenced by the location in the fundus, the presence of signet ring cells, the presence of a lymphoid stroma, the radicalism of the resection, the lymph node invasion, and the percentage of the invaded lymph nodes. In a multivariate analysis, only the presence of signet ring cells reduced survival [Figure 2 and Table 2].

Median disease-free survival was 22 months, with extreme values ranking from 3 to 62 months. The disease-free survival in 1 year, 3 years and 5 years was respectively 82%, 72%, and 70%. Recurrence was observed in ten patients (21.7%).

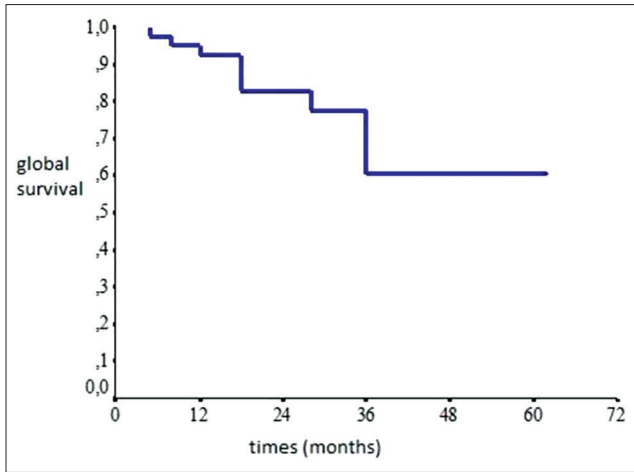


Figure 1: Overall survival rate in the study

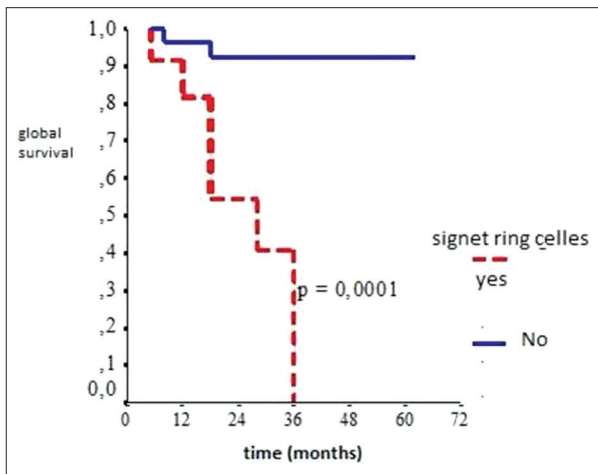


Figure 2: Overall survival if signet ring cells were present

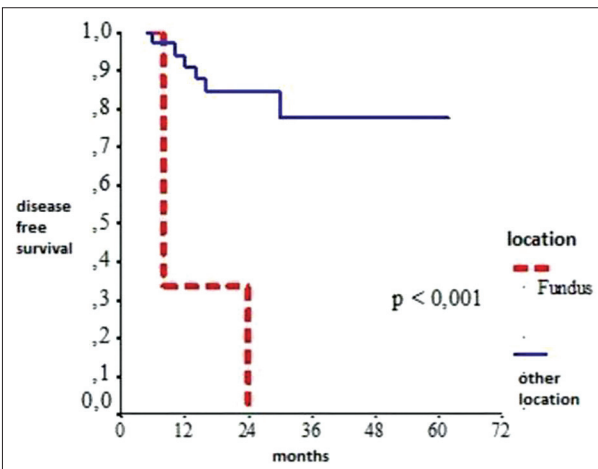


Figure 3: The impact in free disease survival of the location in the fundus

The median period before recurrence was 11 months, with extremes ranking from 3 to 30 months. It was mainly hepatic metastasis in 4 cases and peritoneal carcinosis in 3 cases. Predictors of recurrence in a univariate analysis were the location in the fundus, the subtotal gastrectomy,

Table 1: Factors affecting survival in univariate analysis

Factors	P
Location	0.0083
Fundus	0.0008
Peroperative ascite	0.1120
Peroperative nodes	0.0116
Invasions of adjacent organs	0.0531
Geste (GT vs. GST)	0.0666
Radicalism of the resection	0.0039
Differentiation	0.1154
Lymphoid stroma	0.0001
Signet ring cells	0.0001
Gastric linitis	0.0606
Tumor stage	0.1361
Stade (T1-T2 vs. T3-T4)	0.0512
Lymph node invasion	0.0370
Perineural invasion	0.1088
Vascular embolus	0.0900
Recurrence	0.001
Percentage of the invaded lymph nodes	0.0003

GT: Total gastrectomy, GST: Subtotal gastrectomy

Table 2: Factors influenced global survival in multivariate analysis

	P	RR (OR)	CI RR
Fundus	0.939	627.676	0.008-6.55
Invasions of adjacent organs	0.194	0.288	0.044-1.882
Signet ring cells	0.03	10.689	2.192-52.124
Stage T	0.956	16.160	0.25-3.245
Lymph node invasion	0.940	48.288	5.225-15.24
Percentage of the invaded lymph	0.25	22.58	2.256-245.25
R0 resection	0.354	3.258	3.542-28.36
Stroma lymphoide	0.266	12.25	0.256-78.25

OR: Odds ratio, RR: Relative risk, CI: Confidence interval

the presence of a lymphoid stroma, the gastric linitis, the presence of signet ring cells, an advanced tumoral stage (T3, T4), the lymph node invasion, the percentage of the invaded lymph nodes, and the occurrence of surgical complications.

Based on multivariate analysis, independent factors increasing the risk of recurrence were the location in the fundus (relative risk: 59.3) [Figure 3] the adjacent organs invasion (relative risk: 5.8) [Figure 4], and the lymph node invasion (relative risk: 7.68) [Figure 5].

DISCUSSION

Gastric cancer has a poor prognosis. With the carrying out of standard radical gastrectomy and extended radical gastrectomy, the prognosis of early gastric cancer and resectable advanced gastric cancer has been significantly improved. Prognosis after surgical resection has been widely reported and analyzed in literature.

In this study, global survival was influenced by several factors, such as the location of the tumor, the histological features, and the lymph node invasion. Only the presence

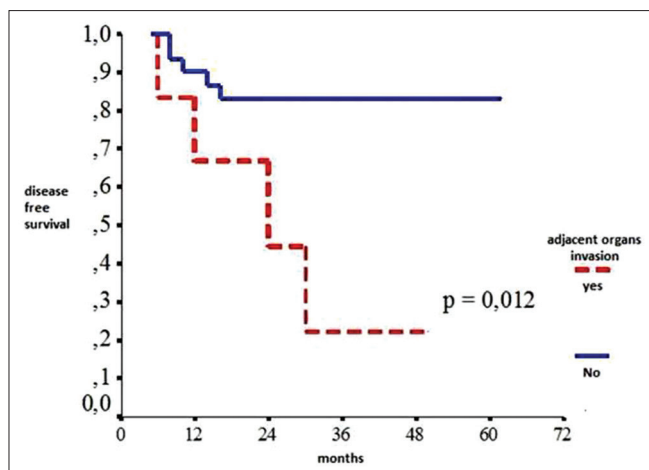


Figure 4: The impact in free disease survival of adjacent organs invasion

of signet ring cells was an independent factor affecting survival. In the literature, several factors were associated to a decrease of global survival.

Prognosis of proximal gastric cancer is poor, even after a curative R0 resection. Probably, it is explained by the delayed diagnosis with an advanced tumoral stage. This fact is clearly mentioned in the retrospective study of Kunisaki, concerning 1245 patients, comparing the proximal location to the other locations.^[4] Indeed, the survival rate at 5 years for the proximal location is 68% versus 83.3% for the other locations ($P < 0.0001$). In the study of Saito, the survival rate of proximal cancers was 78% while it was 84% in distal cancers, with a statistically significant difference.^[5] The degree of parietal invasion is widely conditioning prognosis. Globally, survival is higher of the T1–T2 tumors than those T3–T4. This result is clearly established in this study. Global survival at 5 years was 90% for the T1–T2 tumors versus 30% for the T3–T4 tumors, with a statistically significant difference, based on a univariate study ($P < 0.05$). In most of the studies, the parietal invasion has been identified as an independent factor conditioning survival.^[5,6] In fact, in a recent chinese study, survival at 5 years was 88.1% in T1 tumors versus 27.5% in T4 tumors.^[7]

It is currently admitted that lymph node invasion is the most pejorative prognosis factor.^[8,9] For this reason, a complete and extensive lymph node dissection improves the outlook. In common practice, those dogmas are not always real.

Lymph node invasion in adenocarcinoma is frequent, precocious, and represents unanimously the most pejorative prognosis element.^[10-12] The study and the evaluation of this fact were widely mentioned in the literature, due to the different classifications arising out of the assessment of the lymphatic drainage. Many authors demonstrated that more than 15 taken lymph nodes,^[13,14] and more than 25 for Roder

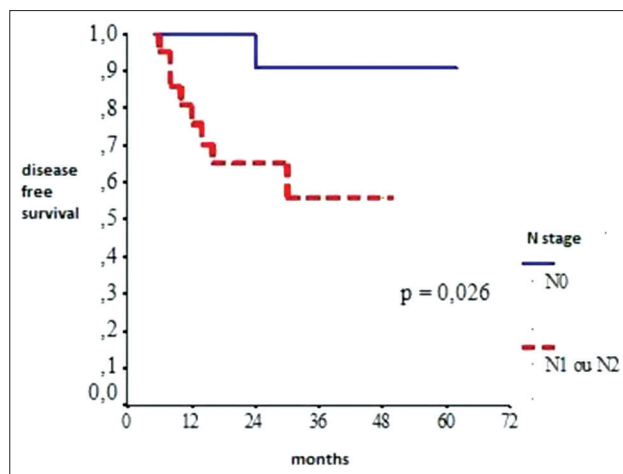


Figure 5: The impact in free disease survival of lymph nodes invasion

et al.^[15] significantly increases survival. This is particularly demonstrated for the stage 3 when the number of taken lymph nodes is higher improved prognosis.^[15]

This seems to indicate that an extensive lymph node dissection can improve significantly the prognosis.

Most of the authors agreed that survival significantly decreases when more than 7 lymph nodes are invaded. For others, the number of invaded lymph nodes is scaled-down and variates from 3 to 4. On the other hand, prognosis is the same for the N2 and the N3 stages. The other histological features mentioned in the literature such as the neural invasion, the vascular, or lymphatic embolus.^[16-19] In some studies, vascular and lymphatic invasion were considered as an independent prognosis factor ($P = 0.013$) as important as the remote metastasis ($P < 0.001$) and the lymph node invasion ($P = 0.033$).^[20] The presence of signet ring cells in the histological examination was considered in most of the studies as a guarded prognosis factor.^[21,22]

In the literature, the disease-free survival at 5 years varies from 0 to 73.8%.^[23-27] The disparity between the rates can be explained by the selective character of some studies. In this study, the disease-free survival was 22 months. Talamonti *et al.*^[28] reported the relation between the disease-free survival and the different histological features. Results showed that the disease-free survival was 47.1% for the N0 tumors while it was 20.6% for the N2–N3 tumors, and 57% for the T1–T2 tumors versus 23.3% in the T3–T4 tumors. In this study, we found the same conclusions. Average period of recurrence in the literature varies from 10.5 to 47 months. In our patient's group, it was 11 months. This average period does not really indicate the exact moment of the recurrence. It would be better to define the recurrence rate. According to Muratore *et al.* study,^[29] the recurrence rate varied in a statistically significant manner related to the tumoral stage (pT1 vs. pT2, $P < 0.001$; pT1 vs. pT3 and 4,

$P < 0.001$; pT 2 vs. pT 3 and 4, $P < 0.006$), to the lymph node invasion (pN 0 vs. pN 1, $P < 0.014$; pN 0 vs pN 2, $P < 0.001$, pN 0 vs. pN 3, $P < 0.001$; pN 1 vs. pN 2, $P < 0.019$; pN 1 vs. pN 3, $P < 0.005$) and to the cumulative percentage of invaded lymph nodes.

Many authors showed interest to compare the early and the late recurrence, and they developed conclusions concerning predictive factors.^[30-32] In those studies, the common element is the lymphatic invasion. It was identified as a risk factor of early recurrence. Other factors have been incriminated, such as the male gender, the vascular embolus, the tumor's size, the types 3 and 4 of Bormann's classification, and the advanced TNM stages. In a Korean study concerning 10783 operated gastric cancers, Kim *et al.*^[33] found 3 independent predictive factors of recurrence: Performing a curative resection, the degree of the parietal invasion and the existence of a lymphatic invasion. In a multicenter prospective study^[34] involving 441 patients operated for a gastric cancer, who underwent a R0 gastric resection; in a multivariate analysis, factors associated to peritoneal recurrence were: The high-grade histological type ($P = 0.023$) the serous membrane infiltration ($P = 0.001$) the lymphatic invasion ($P = 0.023$) and the tumoral size ($P = 0.05$). In the study of Sakar, only lymph nodes were associated with high risk of recurrence in multivariate analysis.^[27] Same findings were observed in other studies.^[35-36]

Predictive factors that are strongly associated with peritoneal recurrence were the histological type and the serous membrane infiltration. A high-grade histological type is associated to a peritoneal recurrence risk at 5 years of 12% a part from any serous membrane infiltration and 69% if the serous membrane is infiltrated.^[34] The same factors have been reported in other studies.^[37] For others authors, positive peritoneal cytology is associated with poor survival and increased peritoneal recurrence in gastric cancer.^[38] The proximal margin is routinely associated with poor prognosis and high local recurrence.^[37,39] But in recent studies of the US gastric cancer if the conversion of a positive intraoperative proximal margin frozen section during gastric cancer resection may decrease local recurrence but it is not associated with improved recurrence-free survival or Overall Survival.^[40] In other studies of multi-institution US gastric cancer group; authors concludes that for resection of proximal gastric adenocarcinoma, proximal margin length is not associated with local recurrence or overall survival. In fact, an R1 margin is associated with advanced N-stage but is not independently associated with recurrence or survival.^[41]

CONCLUSION

Gastric cancer still has a poor prognosis. The knowledge of prognostic factors may improve its management and

the therapeutic care. In this study, independent predictive factors of recurrence were: The location in the fundus, the lymph node invasion, and the invasion of adjacent organs. Improving the prognosis requires an early diagnosis in the stage of superficial cancer and the enlargement of the indications of adjuvant treatments.

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Conflicts of interest

There are no conflicts of interest.

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