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SHORT COMMUNICATIONS

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PROGNOSTIC FACTORS IN METASTATIC GASTRIC CARCINOMA

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Although its incidence has declined over last half-century, gastric cancer remains the second most frequent cause of cancer death in the world. The ⅔ of the patients are metastatic at diagnosis. The current study *aimed* to identify some determinants of survival in patients with metastatic gastric carcinoma. *Materials and Methods*: It was a retrospective study that involved 49 patients treated with palliative chemotherapy between January 2000 and December 2010. Factors included: age, gender, performance status, metastatic diagnosis onset (at diagnosis or later); specific metastatic sites, number of metastatic localizations, response to chemotherapy, and hemoglobin rate. *Results*: In univariate analysis, factors associated to a better survival were: metastasis at diagnosis, good performance status, response to chemotherapy and single metastatic site. Independent factors in multivariate analysis were: metastasis at diagnosis and single metastatic site. *Conclusion*: Our study confirmed many determinants on survival described in the literature.
***Key Words*: gastric cancer, metastasis, chemotherapy, survival, prognostic factors.**

Although its incidence is decreasing in recent decades, gastric cancer is the second leading cause of cancer-related death. It is marked by a large disparity of its impact in terms of geographical distribution: the highest incidences are observed in East Asia (62 new cases/100,000 for men and 26 for women) with lowest rate in North America. In Africa, the estimated incidence is 4.7 new cases/100,000 for men and 3.3 for women) [1]. In Tunisia, gastric cancer represents 4.5% of cancers in men (7th men cancer) and 3.7% of cancers in women (9th women cancer). It represents 24% of digestive cancers [2]. In ⅔ of the patients, gastric cancer is diagnosed at stage IV (unresectable or metastatic tumor). Despite advances in palliative chemotherapy mainly based on cisplatin, the median survival of these patients is around one year. The 5-year survival rate does not exceed 5%. Recently the introduction of trastuzumab in the treatment of tumors expressing Her-2/neu has improved survival rates [3]. Some particularly Asian studies have focused on identifying prognostic factors influencing the survival of metastatic patients in order to improve the different therapeutic approaches. The aim of our study is to identify the parameters correlated with survival in our Tunisian population and to compare them to those described in the literature.

MATERIALS AND METHODS

This is a retrospective study including 49 patients with histological proven gastric cancer treated in the Department of Medical Oncology in the Habib Bourguiba Hospital in southern Tunisia, between January 2000 and December 2010. Our study included patients who had metastases at initial diagnosis of the disease (synchronous metastases) and patients who developed metastatic relapse after initial treatment (metachronous metastases). All patients underwent staging with a physical examination, chest X ray, abdominal ultrasound, thoracoabdominal computed tomography. The treatment consisted in palliative chemotherapy based on cisplatin. Overall survival was calculated from the date of diagnosis to the date of the latest news in synchronous metastatic patients and from the date of relapse in metachronous metastatic patients, according to Kaplan — Meier. We conducted a study of survival with prognostic factors in univariate analysis according to the test of log-rank and multivariate Cox model with significant value for $p \leqslant 0.05$. The factors studied were: sex, age (less than 45 years), the sequence of metastases (synchronous *vs* metachronous), treatment of the primary tumor (gastrectomy), performance status according to the World Health Organization (WHO 0–1 *vs* greater than 1), the number of metastatic sites (unique *vs* multiple), the site of metastases (liver, peritoneum, other), the response to chemotherapy and the hemoglobin level less or greater than 10 g/dl.

RESULTS

Patient characteristics

The mean age was 48.9 years, ranging from 27 to 74 years. There were 30 men and 19 women. Details are presented in Table 1. Thirty-three patients had more than 1st line chemotherapy based on 5-fluorouracil and cisplatin with an objective response rate of 37% and an average time to progression of 7 months. Gastrectomy was performed in 7 patients among 28 patients with synchronous metastases.

Survival and prognostic factors

The median overall survival was 8.6 months. The 1-year, 2-year, 3-year and 5-year survival rate were 26%, 10%, 6% and 2%, respectively (Figure). Prognostic factors for better survival in univariate analysis were: character synchronous metastases, good condition, good response to chemotherapy and single metastatic site. The other studied factors had no impact on survival (Table 2). The synchronous nature of metastases and the single site of metastasis were independent prognostic factors in multivariate analysis (Table 3).

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Table 1. Patient characteristics and disease

	N	%
Sex		
Men	30	61
Women	19	39
Age (median 48.9 years)		
< 45 years	26	53
⩾ 45 years	23	47
Performance status (PS)		
PS 0–1	23	47
PS > 1	26	53
Hemoglobin levels at diagnosis		
< 10 g/dl	22	44
⩾ 10 g/dl	27	56
Chronology of metastases		
Synchronous	28	57
Metachronous	21	43
Seat metastases		
Liver	14	28.5
Peritoneum	23	46.9
Nodes	24	48.9
Lung	6	12.2
Bone and bone marrow	10	20.0
Number of metastatic sites		
One site	15	30.6
Several sites	34	69.4

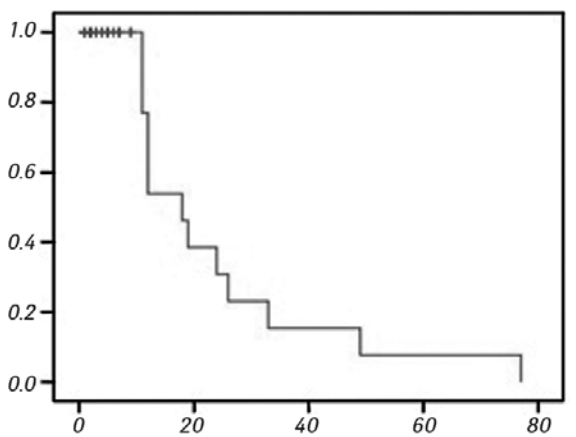

Figure. Overall survival

DISCUSSION

Several authors were interested in studying the prognostic factors and survival in patients with metastatic gastric cancer.

Sex was not identified as a prognostic factor in almost all series. Nevertheless, age less than 50 years or 60 years in the series Kanagavel *et al.* [3] and Yoshida *et al.* [4] was a factor correlated with better survival in univariate analysis. These two factors were not statistically significant in our series.

As in our series, the nature of the site of metastases (liver, peritoneum etc) had no impact on survival in the literature. However, the number of metastatic sites (single or multiple) was a significant factor in both uni- or multivariate analysis varied in the series of Yoshida *et al.* [4] with survival rates at 2 years of 9.5%, 5.4% and 2.9% in case of one site, two or more than three metastatic sites respectively. By cons, this factor has not been found by the other authors [3, 5]. In our patients, the number of metastatic sites showed a significant difference in survival among patients with a single site of metastasis compared with those with multiple metastatic sites ($p = 0.04$).

Table 2. Univariate analysis of survival based on prognostic factors

Factor		1-year overall survival, %	2-year overall survival, %	*p*
Sex	Men	20	9	0.9
	Women	21	15	
Age	< 50 years	23.0	7.6	0.21
	⩾ 50 years	21.7	12.0	
Performance	PS 0–1	32.5	11	0.05
Status	PS > 1	13.0	6	
Hemoglobin level	< 10 g/dl	18	15	0.6
	⩾ 10 g/dl	27	18	
Surgery of the primary tumor (n = 26)	Gastrectomy	28	15	0.26
	No gastrectomy	21	14	
Chronology of metastases	Synchronous	35.7	18.0	0.007
	Metachronous	11.0	0.0	
Number of metastatic sites	Single metastases	40.0	26.6	0.005
	Multiple metastases	17.6	5.0	
Metastatic site	Liver	50	44	0.09
	Peritoneal carcinomatosis	20	11	
	Other	33	19	
Response to chemotherapy	PR ou CR	55	29	
	Stability and progress	17	11	0.05

Table 3. Independent factors in multivariate analysis

Factor	Hazard ratio	*p*
Metachronous metastases	3.7 (0.33–5.6)	0.05
Multiple metastatic sites	4.7 (0.38–6.05)	0.014

In most trials, patients initially and secondarily metastatic are pooled together. From some studies survival data, it appears that among all patients in the metastatic setting, survival is better in case of synchronous metastatic disease versus metachronous metastatic disease with median survival about 12 month [6, 7] and 6 months, respectively [8]. This has been well demonstrated in our series with better survival in synchronous metastatic patients ($p = 0.01$) compared to secondary metastatic patients.

Performance status with a WHO ⩾ 2 is a poor prognosis factor in almost series as well as in multivariate analysis and univariate ones.It represents an independent factor influencing negatively the overall survival [3, 4, 9]. In the series of Chau *et al.* [9] including 1080 patients with metastatic gastric cancer cases treated with different chemotherapy regimens (as part of three randomized Phase III studies), performance status according to WHO at diagnosis was an independent factor of overall survival with a survival significantly deteriorated if WHO ⩾ 2.

In the Japanese series of Yoshida *et al.* [4], the study of survival according to the general state at diagnosis was conducted in 643 patients with metastatic gastric adenocarcinoma. Survival was significantly influenced with a 2-year survival of 11%, 8.5% and 0% for a WHO 0, 1 and 2, respectively. In our series, a performance status greater than 1 was significantly associated with shorter survival with $p = 0.05$.

In advanced disease, gastrectomy is usually done if the patient is symptomatic: tumor stenosis or in case of bleeding. Apart from these situations, palliative gastrectomy is debated.

In a Japanese series including 164 cases of metastatic [10] gastric cancer, palliative gastrectomy was beneficial in case of well-differentiated histology, in the absence of peritoneal metastasis and when surgery is followed or preceded by chemotherapy.

In a Polish retrospective study [11], from 2258 gastrectomy patients, 415 were metastatic. In this series, survival was significantly better in patients undergoing optimal curative gastrectomy to those undergoing non-curative gastrectomy with median survival of 10.6 months and 4.4 months respectively. In the series of Blank *et al*. [5], patients who underwent curative gastrectomy with good histologic response after preoperative chemotherapy, have a good median survival which joins that of non-metastatic patients with a median survival of 35.3 months and a 3-year survival of 47.6%. In the series of Chau *et al*. [9], palliative gastrectomy improved survival and especially the quality of life of patients with gastric adenocarcinoma. In our work, palliative gastrectomy was not associated with a survival benefit.

In a Chinese retrospective series, 39 patients with metastatic gastric tumor were treated with palliative chemotherapy based on 5-fluorouracil and folinic acid. In this study, an objective response to chemotherapy was associated with better survival with median survival of 10.5 months against 5 months in the absence of response [12]. In another study evaluating the FAM protocol for gastric adenocarcinoma in metastatic patients, median survival was 12.5 months in responding patients to treatment *vs* 3.5 months in non responders [13]. In the series of Yoshida *et al.* [4], the good response to chemotherapy was an independent factor for better survival. In our study, an objective response to palliative chemotherapy (complete or partial response) was significantly associated with better survival ($p = 0.01$).

Anemia with a hemoglobin level less than 10 g/dl was an independent factor, in a multivariate analysis, for a low survival in the series of Yoshida *et al*. [4]. This factor was not observed in our series.

CONCLUSION

The factors that have a negative impact on survival reported in the literature are: bad performance status (WHO $\geqslant$ 2), advanced age, multiple metastatic sites, metachronous metastasis, anemia, lack of gastrectomy and poor response to chemotherapy. Independent factors are: bad performance statue, multiple metastatic sites, anemia and poor response to chemotherapy.The majority of these factors were confirmed in our series, particularly metachronous and multiple sites that were found in multivariate analysis.

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors contributed to this article.

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