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ORIGINAL ARTICLE

Surgical treatment of hepatic metastases from gastric cancer

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Abstract
The purpose of the study was to investigate the clinical factors influencing the prognosis of patients submitted to hepatectomy for metastases from gastric cancer and their clinical role. We conducted a retrospective multicentre review. We evaluated how survival from surgery was influenced by patient-related, tumour-related and treatment-related prognostic factors. We analysed data on 144 patients submitted to hepatectomy for metastases from gastric cancer, in the synchronous and metachronous setting. In 117 cases, an R0 resection was achieved, while in 27 an R + hepatic resection was performed. Chemotherapy was administered to 55 patients. Surgical mortality was 2.1% and morbidity 21.5%. One-, 3-, and 5-year OS rates after surgery were 49.9, 19.4 and 11.6%, respectively, with a median OS of 12.0 months. T4 gastric cancer, H3 hepatic involvement, non-curative resection, recurrence after surgery, and abstention from chemotherapy were associated with a worse prognosis. Factor T and H displayed a clear ($p < 0.001$) cumulative effect. Our data show that R0 resection must be pursued whenever possible. The treatment of T4 gastric cancer with hepatic bilateral and diffuse metastasis (H3) should be considered carefully or it should be probably avoided. Finally, a multimodal treatment associating surgery and chemotherapy offers the best survival results.

Keywords Gastric cancer · Hepatic metastasis · Curative surgery

Introduction

In recent years, surgical treatment of hepatic metastases from gastric cancer has been widely discussed in an effort to ameliorate the oncologic results offered by palliative chemotherapy or supportive care [1–18].

We contributed to the debate through previous publications, showing that simple clinical elements may help in the selection of good candidates for surgery, both in the metachronous [19] and in the synchronous [20] setting, and that the possibility to achieve a curative resection is the main prognostic element in this group of patients. Moreover, we found that administration of chemotherapy positively influenced the overall survival of metastatic patients treated with surgery.

In this invited paper, included in an almost monographic issue addressing gastric cancer through different hot topics, we want to present the most recent data concerning the surgical treatment of hepatic metastases from gastric cancer obtained from the analysis of the experience of the major Institutions participating in the Italian Gastric Cancer Research Group.

Methods

We retrospectively reviewed the data of 144 gastric cancer patients submitted to surgical treatment for both synchronous and metachronous hepatic metastases from 1990 to January 2017. The data were extrapolated from a prospectively collected multicentric database, shared by six institutions,

The article is part of topical collection on Gastric Cancer Surgery.

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members of the Italian Research Group on Gastric Cancer. Data were managed according to institutional rules with patient consent.

Preoperative workup systematically included computed tomography, while hepatic MRI and staging laparoscopy were not routinely employed, particularly for patients treated before 2010. Patients with preoperative evidence of direct infiltration of the hepatic parenchyma from the gastric primary were not considered as well as those with extrahepatic metastases identified before surgery.

Pathologic data concerning the gastric primary were collected as suggested by the General Rules of the IGCA and classified following the 7th AICC-TNM system. The extent of hepatic involvement was classified according to the JGCA H grading of liver involvement [21].

Follow-up was structured as already described [22] and stopped on 1 June 2017. We evaluated how survival from diagnosis was influenced by patients-, gastric cancer-, metastasis-, and treatment-related prognostic factors, as detailed in Table 1.

Statistical analysis

Descriptive statistics are presented as median and interquartile range (IQR 25–75%) or confidence interval (CI). Comparisons between groups were obtained through Chi square analysis for discrete variables and through *t* Student's test analysis for continuous variables. Overall survival (OS) was measured from the date of resection to the date of death or the latest follow-up. Survival curves were generated by the Kaplan–Meier method, and statistical significance was determined using the log-rank test. Only variables that were statistically significant ($p < 0.05$) at univariate analysis were considered for multivariate analysis with Cox proportional hazards model.

Results

In this study, we considered 144 patients, 94 males and 50 females. Median age was 68 years (IQR 59.5–75 years). One-hundred and twelve patients (77.8%) presented synchronous hepatic metastases at the diagnosis of gastric cancer, while 32 (22.2%) developed metachronous hepatic metastases after curative gastrectomy.

Gastric cancer was treated in all patients with radical surgery, associated in 75.7% of cases to D2 lymphadenectomy; D1 lymphadenectomy was performed in 11 patients (7.6%), as well as D3 lymphadenectomy. Hepatic resection was achieved by single or multiple metastasectomy in 108 cases (75.0%), segmentectomy/bisegmentectomy in 24 cases (16.7%), and major hepatic resection in 12 (8.3%). In the synchronous setting, 13 patients (11.6%) also had other extrahepatic metastases, detected at laparotomy: in 6 cases limited peritoneal metastases and in 7 cases distant intraabdominal lymphonodal metastases. In five cases, these extrahepatic metastases were resected.

Table 1 Clinical characteristics of the population

Characteristics	*n*	%
Sex		
Male	94	65.3
Female	50	34.7
Gastric cancer location		
Upper	48	33.3
Body	45	31.3
Distal	25	17.3
Linitis	2	1.4
Stump	3	2.1
x	21	14.6
pT		
T1–T2	23	16.0
T3	27	18.8
T4	66	45.8
x	28	19.4
pN		
N0–N1	48	33.3
N2	14	9.7
N3	54	37.5
x	28	19.4
Histology		
Intestinal	77	53.5
Diffuse	24	16.7
Other	16	11.1
x	27	18.8
Grading		
G1	0	0.0
G2	13	9.0
G3	22	15.3
x	109	75.7
Timing of hepatic metastases		
Synchronous	112	77.8
Metachronous	32	22.2
Extent of hepatic involvement		
H1	100	69.5
H2	29	20.1
H3	15	10.4
Extrahepatic metastases		
Yes	13	9.0
No	131	91.0
Location of extrahepatic metastases		
Peritoneal	7	4.9
Lymphonodal	6	4.2

A radical resection (R0) was obtained in 117 cases (81.2%), while a microscopically (R1) or macroscopically (R2) non-curative resection was obtained in 14 (9.7%) and 13 cases (9.1%), respectively. The most common reasons for non-curative resection were unexpected intraoperative upstaging of the factor H, the critical position of hepatic lesion/s, and the presence of other extrahepatic metastasis.

Postoperative complication rate was 21.5% and three patients (2.1%) died during the postoperative period (Table 2).

In the synchronous setting, preoperative chemotherapy was administered in 16 cases (14.3%); 28 patients (25.0%) received postoperative chemotherapy, while 4 patients (3.6%) received both pre- and postoperative chemotherapy. Among patients treated with postoperative chemotherapy (alone or associated with preoperative treatment), seven (21.2%) had not received a curative resection. With regard to patients with metachronous hepatic metastases, chemotherapy was administered only in seven cases (22.6%).

Twenty-six patients (18%) were alive at the time we stopped follow-up; 22 of them had no tumour relapse, while 4 had haematogenous recurrence. Five patients died due to other causes than tumour recurrence and six patients were lost at follow-up. One-hundred and eleven patients (77.1%) died because of gastric cancer recurrence. This was haematogenous in 42 cases, peritoneal in 5, and in the regional nodes in 4; the details of recurrence were unknown in 60 cases.

One-, 3-, and 5-year OS rates after surgery were 49.9, 19.4, and 11.6%, respectively (Fig. 1), with a median OS of 12.0 months (CI 95% 8.7–15.3).

At univariate analysis, the factors that proved to have an impact upon survival were: factor T of gastric primary, the extent of hepatic involvement (factor H), the timing of hepatic metastases (synchronous vs metachronous), the curative effect of surgery, the recurrence of the disease, and the administration of chemotherapy. At multivariate analysis, all these factors except the timing of hepatic metastases were confirmed (Table 3). In detail, T4 gastric cancer, H3 hepatic involvement, non-curative resection, recurrence after surgery, and the abstention from chemotherapy were associated with a worse prognosis. Factors T and H are the sole clinical factors that may be considered in a preoperative phase in the selection of patients to be submitted to surgery; they displayed a clear ($p < 0.001$) cumulative effect.

Table 2 Details of treatment

Characteristics	*n*	%
Gastrectomy		
Total	71	49.3
Subtotal	42	29.2
Stump resection	2	1.4
x	29	20.1
Lymphadenectomy		
D1	11	7.6
D2	109	75.8
D3	11	7.6
x	13	9.0
Curative effect of surgery		
R0	117	81.3
R1	14	9.7
R2	13	9.0
Type of hepatic resection		
Metastasectomy	108	75.0
Segmentectomy	24	16.7
Major resection	12	8.3
Resection of extrahepatic metastases		
Yes	5	38.5
No	8	61.5
Chemotherapy		
None	96	66.7
Preoperative	16	11.1
Postoperative	28	19.4
Pre- and postoperative	4	2.8
Type of preoperative chemotherapy (synchronous)		
Fluorouracil	0	0.0
Fluorouracil + platinum	2	12.5
Fluorouracil + taxanes	1	6.2
Other	13	81.3
Type of postoperative chemotherapy (synchronous)		
Fluorouracil	3	10.7
Fluorouracil + platinum	5	17.8
Fluorouracil + taxanes	2	7.2
Other	18	64.3
Postoperative morbidity		
Yes	31	21.5
No	113	78.5
Postoperative mortality		
Yes	3	2.1
No	141	97.9

Discussion

Our analysis shows that the extension of gastric primary (factor T) and the extension of hepatic disease (factor H) are the only clinical factors that influence survival in the subgroup of gastric cancer patients with hepatic metastasis. These factors were already found to have a prognostic role in this subgroup of patients [3, 9, 11, 20]; we confirm that there are very few clinical factors that can drive the selection of the best candidates for surgery in the metastatic setting of gastric cancer. The other prognostic factors that emerge from our analysis are the curative

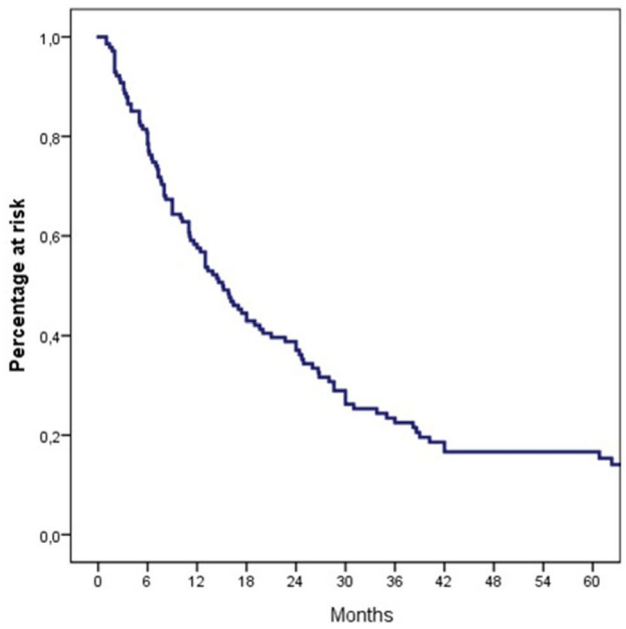

Fig. 1 Overall survival

effect of surgery, recurrence of disease, and administration of chemotherapy.

In a recent meta-analysis from Markar et al. [23] that analysed 39 studies on 991 patients treated with hepatic resection for gastric cancer metastases, the number of hepatic metastases and the type of liver involvement, the factor T and N of gastric primary, the vascular invasion, and the curative effect of surgery were reported as prognostic factors. The prognostic role of the factor T of the gastric primary, negative when rated T4, is widely recognized [3–8]. Indeed, the serosal involvement is a watershed between a neoplasm still theoretically limited into the gastric wall and one with diffusive potential to the peritoneal cavity. As regard the prognostic role of the hepatic tumour burden (factor H), a general consensus exists. Besides all biological considerations, it is worth noting that in H3 patients the percentage of non-curative resection was higher than in the H1–H2 group (40 vs 17.3%, respectively). Factors T and H displayed a cumulative negative impact upon survival: it dropped actually from 30 months in the case of T1–T3 and H1–H2 disease to 7.3 months for T4 and H3 patients ($p < 0.001$).

Our data confirm that the complete surgical removal of tumor bulk (both gastric tumor and hepatic metastasis) is a major prognostic factor and it suggests that no efforts must be spared to achieve it, also referring to non-surgical ablative techniques [4, 24, 25]. Median survival is 17 months

Table 3 Prognostic factors: univariate and multivariate analysis (only variables significant at univariate analysis are shown)

Prognostic variables	*n*	Median survival (months)	95% CI	Univariate *p* value	Multivariate *p* value	Hazard ratio	95% CI
pT				0.001	0.025	3.8	1.4–10.8
T1–T2	21	5.0	16.9–53.1				
T3	27	20.0	6.4–33.5				
T4	65	10.2	6.5–13.8				
Timing of hepatic metastases				0.004	n.s.		
Synchronous	109	11.2	7.6–14.7				
Metachronous	32	31.0	22.6–39.3				
Hepatic involvement				< 0.001	0.021	2.8	1.3–6.1
H1	98	17.0	9.6–24.3				
H2	28	14.4	2.8–25.9				
H3	15	7.3	3.9–10.7				
Curative effect				< 0.001	0.010	5.8	1.8–15.8
R0	15	17.0	12.1–21.9				
R1	13	6.6	5.6–7.5				
R2	13	8.0	4.9–11.1				
Chemotherapy				0.030	< 0.001	3.8	2.0–7.4
Yes	55	24.0	16.1–31.9				
No	86	13.0	9.9–16.1				
Recurrence				< 0.001	0.002	10.3	2.3–46.5
No	19	116.0	99.3–132.7				
Yes	61	11.2	6.9–15.4				

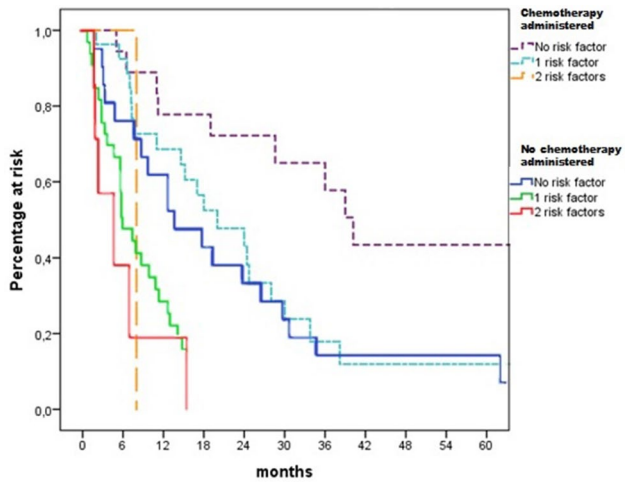

Fig. 2 Influence of chemotherapy on survival according to the presence of risk factors

after curative surgery, but drops to 7 months in the case of R + resection, which is similar to the median survival of patients submitted to palliative surgery or to supportive treatments [19, 20]. Our data on the role of curative surgery confirms those reported by some European authors [12, 15, 26], but are in contrast with those reported by Cheon et al. [24], who observed no significative differences in survival performances after R0 or R + resections. This can be probably explained by the positive impact of chemotherapy that was administered to a higher percentage of patients (88 vs 33.3%) in the Korean series. Moreover, we should consider the role of the different biologies of gastric cancer in Eastern and Western countries. Due to the retrospective nature of our study, it was difficult to analyse factors related to tumour biology, but we are well aware that further study is needed to examine this point [23, 27]. It is important to highlight that the surgical treatment of these patients should be referred to tertiary centres as the ones involved in our study, where postoperative morbidity and mortality rate can be minimized.

The beneficial role of chemotherapy upon survival can be explained by the fact that hepatic metastases are expression of haematogenous diffusion; therefore, they can take advantage of systemic treatment before or after surgical debulking. It is well known that a multidisciplinary approach is needed for the treatment of metastatic patients [15, 24, 28], but the timing of chemotherapy is still a matter of discussion, both for the treatment of non-metastatic and metastatic patients.

Chemotherapy displayed in this study a clear survival benefit (24.0 vs 13 months) and all the long-term survival patients had received chemotherapy. In Fig. 2 we show the huge impact of chemotherapy upon survival, dividing the study population into two groups: those who received chemotherapy and those who did not. Chemotherapy ameliorates survival also for patients with negative prognostic factors as T4 and H3 tumors, pushing the survival curve at the level of patients without risk factors who did not receive chemotherapy. At contrary, there are no survival chances for patients presenting risk factors if they do not receive systemic treatment.

Due to lack of data, we could not analyse the role of response to chemotherapy but we would like to prompt the collection of these data for further studies.

As could be expected, recurrence after surgery impacts unfavourably upon survival. Interestingly, 55.7% of patients who developed recurrence had not received chemotherapy and the absence of chemotherapy proved to be a risk factor for the development of disease recurrence (HR 2.9 CI 95% 2.7–4.9; $p < 0.001$).

Our data do not allow an insight into the respective role of neoadjuvant and adjuvant chemotherapy in this subset of patients. This point will be focused on soon.

Conclusion

We can state that the surgical treatment of hepatic metastasis from gastric cancer should be taken into consideration after careful evaluation of each single case, as only a radical approach with curative intent is worthy. Moreover a multidisciplinary treatment is necessary, as chemotherapy plays a fundamental role in the metastatic setting of the disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Research involving human participants and/or animals The study was approved by Institutional Review Board.

Informed consent All patients signed at the admission a consent to anonymous data treatment for retrospective studies.

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