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## A pragmatic approach improves the clinical management of stage IV gastric cancer: Comparison between the Meta-Gastro results and the GIRCG's retrospective series

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## ABSTRACT

**Introduction:** The Italian Research Group for Gastric Cancer developed a prospective database about stage IV gastric cancer, to evaluate how a pragmatic attitude impacts the management of these patients.

**Materials and methods:** We prospectively collected data about metastatic gastric cancer patients thanks to cooperation between radiologists, oncologists and surgeons and we analyzed survival and prognostic factors, comparing the results to those obtained in our retrospective study.

**Results:** Three-hundred and eighty-three patients were enrolled from 2018 to September 2022. We observed a higher percentage of laparoscopic exploration with peritoneal lavage in the prospective cohort. In the registry only 3.6 % of patients was submitted to surgery without associated chemotherapy, while in the retrospective population 44.3 % of patients were operated on without any chemotherapy. At univariate and multivariate analyses, the different metastatic sites did not show any survival differences among each other (OS 20.0 vs 16.10 vs 16.7 months for lymphnodal, peritoneal and hepatic metastases, respectively), while the number of metastatic sites and the type of treatment showed a statistical significance (OS 16,7 vs 13,0 vs 4,5 months for 1, 2 and 3 different metastatic sites respectively,  $p < 0.001$ ; 24,2 vs 12,0 vs 2,5 months for surgery with/without chemotherapy, chemotherapy alone and best supportive treatment respectively,  $p < 0.001$ ).

**Conclusions:** Our data highlight that the different metastatic sites did not show different survivals, but survival is worse in case of multiple localization. In patients where a curative resection can be achieved, acceptable survival rates are possible. A better diagnostic workup and a more accurate staging impact favorably upon survival.

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## 1. Introduction

Gastric cancer is diagnosed at stage IV in 35–55 % of cases in Western countries [1], and median disease survival at this stage is about 10 months [2]. Recently, many retrospective studies demonstrated that a multidisciplinary approach, including chemotherapy and curative surgery both on stomach and metastases, can be offered to patients with good results in term of survival [3–12].

The Italian Research Group on Gastric Cancer developed an observational prospective database on stage IV gastric cancer, with the purpose of collecting data as homogeneously as possible and overcoming potential biases connected to the retrospective study. Moreover, we tried to compare the preliminary results of the registry data with the results of our previously published retrospective study about stage IV gastric cancer [13], in order to understand how a pragmatic attitude, such as the one indirectly promoted by our study, impacts the management of metastatic gastric cancer patients.

## 2. Materials and methods

Data regarding stage IV gastric cancer at diagnosis have been collected prospectively from 2018 in an Italian multicentric registry, called “MetaGastro”. Twelve high volume referral centers are participating in registry editing. Data were managed according to institutional rules with patient consent. This observational research was approved by the ethical committee of the leading center.

Information about the gastric tumor, the metastases, the treatment and the follow-up have been gathered thanks to cooperation between radiologists, oncologists and surgeons from each center. The registry has been built after multidisciplinary discussion and it includes more than 100 fields, detailing information about staging, restaging and treatment in order to obtain a precise classification of the disease and to better evaluate the outcomes. Radiological images of all patients have been evaluated by an expert team of dedicated radiologists in order to better identify site and characteristics of the metastases and the response to treatment.

Data collection for the present study refers to the period September 2018–September 2022. We obtained an unselected population of 383 metastatic gastric cancer patients. Patients received chemotherapy followed by surgery (either with curative or palliative intent) or chemotherapy alone or surgery with/without postoperative chemotherapy or best supportive care according to general conditions, extent of metastatic disease or patients’ preference. In case of preoperative chemotherapy, restaging CT was always performed. We analyzed data regarding patients’, tumor’s and metastases’ characteristics in order to look for prognostic factors for survival and we compared the results to those obtained in our retrospective study.

### 2.1. Statistical analysis

Descriptive statistics are presented as median and interquartile range (IQR, 25%–75 %) or confidence interval (CI). Different study groups were compared by means of  $\chi^2$  or t-student test for discrete or continuous variables, respectively. Statistical significance was rated at  $p < 0.05$ . Overall survival (OS) was measured from the date of diagnoses to the date of death or latest follow-up. Survival curves were generated by the Kaplan–Meier method and compared by log-rank test. Variables that resulted to be statistically significant ( $p < 0.05$ ) at univariate analysis were considered for multivariate analysis with a Cox proportional hazards model. All statistical analyses were performed by means of SPSS 26.0 – IBM, New York, NY.

## 3. Results

Three-hundred and eighty-three patients were enrolled in the prospective registry from September 2018 to September 2022. Median age

was 69 years old (IQR 59–75 y.o.). Diagnosis was obtained in all cases by means of esophagogastroduodenoscopy with histological confirmation and all patients were staged by total body CT scan.

Details of retrospective and prospective cohort of patients are presented in Table 1. Surgical exploration was performed in about 40 % of cases in both groups, but we registered a higher percentage of laparoscopic exploration with peritoneal lavage and cytology in the prospective cohort (34 % and 34.5 % vs 16 % and 16.3 %, respectively), while in the retrospective the majority of explorations was laparotomic. This reflects a change in the accuracy of preoperative study and selection of metastatic patients, with better adhesion to guidelines’ recommendations [14].

The number of patients with multiple metastatic sites is greater in the Meta-Gastro (34.8 % vs 26.6 %), mirroring the wider origin of these patients compared to the retrospective study, where only patients from surgical cohorts were enrolled. On the contrary, many of the Meta-Gastro patients come from medical oncology datasets, overcoming possibly selection biases that could be present in our previous study.

As regard chemotherapy, we note that the vast majority of prospective registry’s patients received a chemotherapy treatment, alone or combined to surgery, and only 3.6 % was submitted to surgery without pre- or post-operative chemotherapy. Conversely, in the retrospective population 44.3 % of patients were operated on without any chemotherapy. This is another important sign of improvement in the management and care of metastatic patients, with a higher collaboration among different specialists in multidisciplinary teams. On the other hand, we reported a great variability in the chemotherapeutical regimens among different centers, both in the retrospective and prospective studies.

Table 2 reports data about clinical staging according to TNM 8th edition [15] in both populations. In the registry we noted a higher percentage of patients in whom the radiological TNM is not available at

**Table 1**  
Characteristics of retrospective and prospective populations.

	Retrospective cohort (282 patients)		Prospective registry cohort (383 patients)	
	Nr.	%	Nr.	%
<b>Histology</b>				
Adenocarcinoma NOS <sup>a</sup>	–	–	164	<b>42,8</b>
Diffuse/poorly cohesive/signet ring cell	122	<b>43,2</b>	129	<b>33,7</b>
Intestinal/tubular	112	<b>39,7</b>	74	<b>19,3</b>
Mixed	41	<b>14,5</b>	6	<b>1,6</b>
Other	7	<b>2,6</b>	10	<b>2,6</b>
<b>Surgical exploration</b>				
None	176	<b>62,4</b>	227	<b>59,3</b>
Laparoscopic	44	<b>15,6</b>	130	<b>33,9</b>
Laparotomic	62	<b>22,0</b>	26	<b>6,8</b>
<b>Cytology</b>				
Not performed	236	<b>83,7</b>	251	<b>65,5</b>
Positive	21	<b>7,4</b>	48	<b>12,6</b>
Negative	25	<b>8,9</b>	84	<b>21,9</b>
<b>Site of metastases</b>				
Distant lymph nodes	32	<b>11,3</b>	58	<b>15,1</b>
Peritoneal	126	<b>44,7</b>	125	<b>32,6</b>
Hepatic	45	<b>16,0</b>	62	<b>16,2</b>
Hematogenous extra-abdominal	4	<b>1,4</b>	5	<b>1,3</b>
>1 site	75	<b>26,6</b>	133	<b>34,8</b>
<b>Yoshida’s classification</b>				
1	–	–	44	<b>11,5</b>
2	–	–	131	<b>34,2</b>
3	–	–	108	<b>28,2</b>
4	–	–	100	<b>26,1</b>
<b>First line treatment</b>				
Chemotherapy alone	–	–	224	<b>58,5</b>
Chemotherapy + surgery	157	<b>55,7</b>	118	<b>30,8</b>
Best support treatment	–	–	27	<b>7,1</b>
Surgery without chemotherapy	125	<b>44,3</b>	14	<b>3,6</b>

<sup>a</sup> Not otherwise specified.

centralization.

Considering the intention to treat, we noted a higher rate of patients addressed to curative resection in the retrospective study (74,1 % vs 65,9 % of the 132 patients of Meta-gastro that have been submitted to surgery). However, the percentage of curative (R0) resections is greater in the MetaGastro (56,1 % vs 41,5 %).

Twenty-six percent of patients in the retrospective cohort developed complications after surgery, while this percentage was lower in the registry (Table 3).

Table 4 resumes the prognostic factors' analyses. At univariate and multivariate analyses, the number of metastatic sites and the type of treatment showed a statistical significance (OS 16,7 vs 13,0 vs 4,5 months for 1, 2 and 3 different metastatic sites respectively,  $p < 0.001$  – Fig. 1; OS 24,2 vs 12,0 vs 2,5 months for surgery with/without chemotherapy, chemotherapy alone and best supportive treatment respectively,  $p < 0.001$  - Fig. 2). Both in the retrospective and prospective population the site of the metastases did not display a significant role in affecting survival: OS was 20.0 months in case of lymphnodal metastases, 16.1 months for peritoneal metastases and 16.7 months for hepatic metastases,  $p = 0.239$  (prospective registry); in the retrospective series the OS was 9.8, 11.2 and 11.6 months for lymphnodal, peritoneal and hepatic metastases, respectively ( $p = 0.835$ ). We also performed univariate and multivariate analyses in the subgroup of patients who received surgical treatment and the type of surgery confirmed its statistical value (OS 33,7 vs 25,5 vs 13,4 vs 9,9 months for curative surgery, conversion surgery, palliative surgery and non resective palliation respectively,  $p < 0,001$  – Fig. 3).

#### 4. Discussion

To the best of our knowledge this is the first attempt to collect data about a wide, unselected population of metastatic gastric cancer patients for the purpose of obtaining a clear picture of this disease and its management. In our previous paper “Stage IV Gastric Cancer: The Surgical Perspective of the Italian Research Group on Gastric Cancer” we published the results of a retrospective series of patients observed and treated in surgical institutions, demonstrating that in this subset of patients a possibility for effective care exists [13]. The key points of the study were represented by the survival advantage in patients submitted to curative surgery, the absence of survival differences according to different metastatic sites and the absence of metastases-related variables capable to predict survival.

The analyses of data from the prospective registry show an

**Table 2**  
Details of surgical treatment.

	Retrospective cohort (282 patients)		Prospective registry cohort (132 patients submitted to surgery)	
	Nr.	%	Nr.	%
<b>Type of surgery</b>				
Palliative resection	66	<b>23,4</b>	29	<b>22,0</b>
R0 resection (resectable ab initio)	164	<b>58,2</b>	49	<b>37,1</b>
Conversion surgery	45	<b>15,9</b>	38	<b>28,8</b>
Non resective surgical palliation	7	<b>2,5</b>	16	<b>12,1</b>
<b>Curativity of surgery</b>				
R0	117	<b>41,5</b>	64	<b>48,5</b>
R1	75	<b>26,6</b>	16	<b>12,1</b>
R2	90	<b>31,9</b>	42	<b>31,8</b>
Rc0 <sup>a</sup>	-	-	10	<b>7,6</b>
<b>Postoperative complication (Clavien-Dindo)</b>				
0-1-2	208	<b>73,8</b>	109	<b>82,6</b>
3a	60	<b>21,3</b>	12	<b>9,1</b>
3b	8	<b>2,8</b>	6	<b>4,5</b>
4	6	<b>2,1</b>	3	<b>2,3</b>
5	0	<b>0</b>	2	<b>1,5</b>

<sup>a</sup> Complete clinical regression after chemotherapy.

**Table 3**

Clinical staging according to 8th edition of TNM.

	Retrospective cohort (282 patients)		Prospective registry cohort (383 patients)	
	Nr.	%	Nr.	%
<b>cT</b>				
1-2	15	<b>5,3</b>	11	<b>2,9</b>
3-4	249	<b>88,3</b>	231	<b>60,3</b>
X	18	<b>6,4</b>	141	<b>36,8</b>
<b>cN</b>				
0	54	<b>19,2</b>	23	<b>6,0</b>
1	208	<b>73,7</b>	285	<b>74,4</b>
X	20	<b>7,1</b>	75	<b>19,6</b>

improvement in the preoperative workup in the metastatic setting, with higher number of staging laparoscopy and peritoneal cytology, and an increased percentage of patients that received chemotherapy in association to surgery.

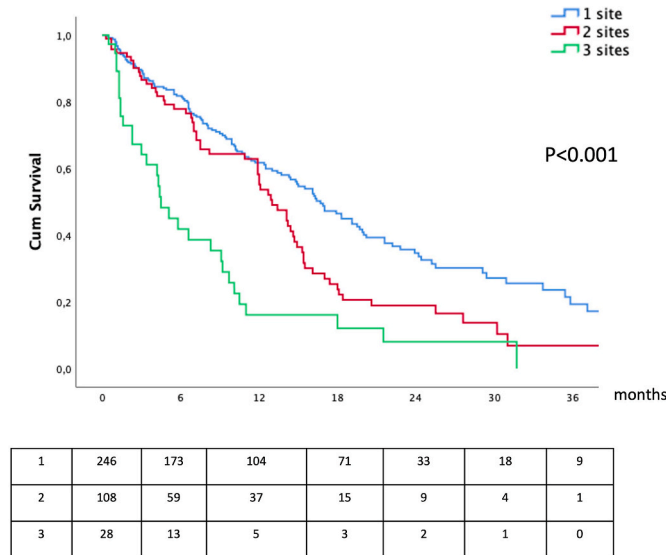
Moreover, our analyses confirmed a clear survival advantage for those patients who can receive a curative treatment both on gastric cancer and metastases. This advantage is evident also in patients that are submitted to conversion surgery, that is to say, patients that were judged not operable with curative intent at the first evaluation but who became operable after one or more chemotherapy cycles. In the retrospective cohort the median survival of R0, R1 and R2 patients was 14.0, 8.3 and 7.5 months respectively, while in the unselected prospective population the median survival of patients submitted to curative resection (R0) was 33.7 months for patients considered resectable at first evaluation and 25.5 months for conversion surgery group; survival drop to 13.4 and 9.9 months respectively for palliative resection and palliative surgery without resection. These results are in line with those reported in Literature [16–18], highlighting, on one side, the good performances of metastatic patients in whom curative (R0) resection can be achieved and, on the other, the favorable effects of the multidisciplinary approach, which promotes specific treatment to a greater percentage of patients. Consistent with this finding is the reduced complication rate observed in the subgroup of patients submitted to surgery. The data of the prospective registry are more representative of the metastatic gastric cancer population compared to those of our retrospective study, as in the former we included all patients presenting at diagnosis with any metastases from gastric cancer and not only the subgroup of patients that received a surgical treatment or a surgical palliation. We can confirm that even in the metastatic setting a chance of curativity can be given to patients and for this purpose a careful selection must be done. However, the site of the metastases should not be used as criterion of selection, because our data confirm that survival is not influenced by the different metastatic sites, as it already appeared in the retrospective study. On the contrary, the presence of more than one metastatic site affects negatively the median survival of the population. Although a single metastatic site offers better survival chances [19–22], we found some long-term survivors also in case of 2 different metastatic sites.

In the registry data analyses we did not find prognostic factors related to gastric tumor, although we highlighted the prognostic role of the number of metastatic sites, Yoshida's classification and type of treatment received. In the Literature there are many reports referring to prognostic factors in stage IV gastric cancer which show a variety of results, such as performance status, histological type, tumor size, number of non-curative factors, curativity of surgery (R0), pathological response, pN status, and postoperative chemotherapy [23–32]. We believe that it in future patient's selection should be guided by sensitive biomarkers, because most of the prognostic factors mentioned above are available only after evaluation of a surgical specimen and, therefore, they are not always available in the metastatic setting.

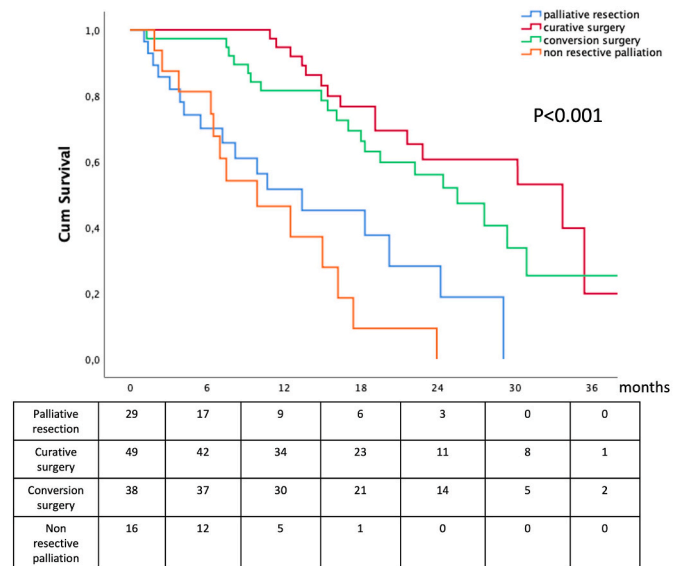
Moreover, for an accurate patients' selection a strict collaboration between a dedicated team of radiologists, oncologists and surgeons is mandatory. As mentioned in result section, in the registry we found a

**Table 4**  
Results of univariate and multivariate analyses.

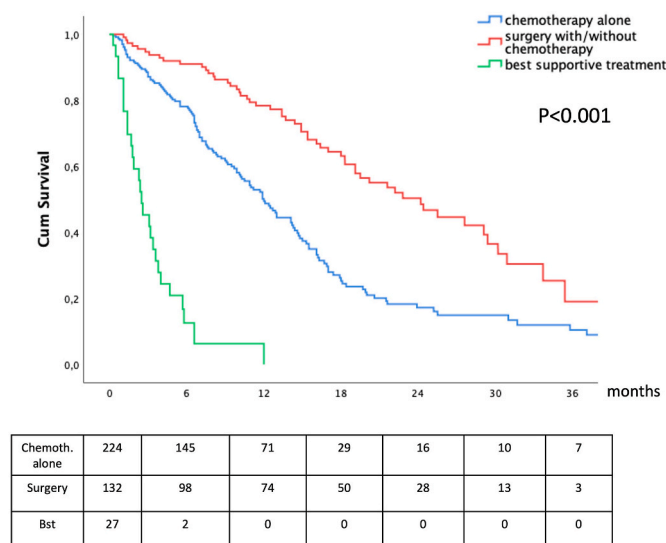
	Retrospective cohort (282 patients)			Prospective registry cohort (383 patients)		
	p-value univariate	p-value multivariate	Odds ratio ±95 % CI	p-value univariate	p-value multivariate	Odds ratio ±95 % CI
Lymphadenectomy	<0.001	<0.001	0.5 (0.4–0.8)	Ns	Ns	-
Curativity	<0.001	<b>0.0032</b>	1.6 (1.1–2.3)	<0.001	Ns	-
Gastric margin	<0.001	Ns	-	-	-	-
pT	<0.001	Ns	-	0.233	Ns	-
pN	<0.001	<b>0.003</b>	1.0 (0.9–4.0)	0.064	Ns	-
Nr. Resected nodes	0.048	<b>0.028</b>	0.07 (0.20–0.03)	-	-	-
Histology	0.015	<b>0.023</b>	1.7 (1.1–2.5)	0.588	Ns	-
Yoshida’s classification	-	-	-	0.038	Ns	-
Type of surgery	-	-	-	<0.001	<b>&lt;0.001</b>	<b>0.3 (0.2–0.6)</b>
Nr. of metastatic sites	-	-	-	<0.001	<b>&lt;0.001</b>	<b>0.4 (0.3–0.7)</b>



**Fig. 1.** Survival according to the number of metastatic sites.



**Fig. 3.** Survival according to the type of surgical treatment.



**Fig. 2.** Survival according to the treatment received.

high percentage of patients in whom radiological TNM was not available, reflecting the fact that many CT scans at diagnosis are performed in low-volume centers, before patients’ centralization, without a dedicated radiologist expert in the evaluation of gastric tumor extension and nodal

involvement. To overcome this bug in classification, all CT of Meta-Gastro patients are under re-evaluation by expert radiologists and in the near future these data will be available for further consideration. The CT revision can help to identify correctly the sites and number of metastases and each case should be discussed with the oncologists to better establish the therapeutical steps. A correct disease’s stadiation, actually, allow to treat more appropriately homogenous groups of patients, avoiding over- or under-treatments. Another cornerstone of metastatic patients’ management is the surgical exploration, that should be laparoscopic whenever possible. Exploration helps to quantify the metastatic disease in the abdomen and, together with the CT scan, allow to submit patients to the correct type of treatment.

**4.1. Limits of the study**

This is a preliminary report of data from a prospective registry about stage IV gastric cancer. Some data are not yet available, as results of radiological revision of CT scans. Moreover, in some cases data are not homogenous, reflecting the heterogeneity of real-life approach to metastatic patients, as in case of the choice of the chemotherapy regimens.

**5. Conclusions**

Our data show that even in metastatic patients, whenever a curative resection can be achieved, acceptable survival rates are possible. The different metastatic sites did not present different survival among each other, but survival is worse in case of multiple metastatic sites. We

recommend the management of stage IV gastric cancer in a multidisciplinary tumor-board with participation of dedicated team of radiologists, oncologists and surgeons to better identify patients with a load of metastatic disease in whom a curative surgery can reasonable be obtained.

### Declaration of competing interest

All authors have no competing interests to declare.

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