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Review

The Role of Surgery in the Treatment of Metachronous Liver Metastasis from Gastric Cancer: A Systematic Review

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Abstract. *Background: Few data are available regarding metachronous liver metastases from gastric cancer. We aimed to identify data regarding the survival of these patients, considering the chosen treatment, with particular attention to the role of surgery. Materials and Methods: A systematic review was carried out from 2000 to 2020. We chose articles reporting data from patients with metachronous liver metastases after curative gastrectomy. Data regarding 1-, 3- and 5-year overall survival were analyzed. Results: Survival was improved in patients eligible for surgery (absence of extrahepatic non-curative factors and feasible complete macroscopic removal of liver deposits, i.e., H1 and H2 liver involvement, metastases less than 5 cm in size) when curative liver resection was performed, with a median overall survival of 24 months (vs. 3.13 in patients treated with chemotherapy). N Status, extent and maximum size of liver metastases, and hepatic surgical treatment were identified as independent prognostic factors. Conclusion: Selected patients with metachronous liver metastases from gastric cancer may benefit from multimodal 'aggressive' treatment. When hepatic involvement is limited (H1 and H2) and the size of metastases less than 5 cm, surgery was shown to increase survival.*

Gastric cancer is a global health problem. Although its incidence and mortality have decreased due to early diagnosis and more effective treatments, more than 1 million people are diagnosed with gastric cancer worldwide each year (5.7% of all cancer cases diagnosed) (1). Gastric cancer remains the third-leading cause of cancer-related death (2). In the Far East, the highest incidence rates are reported (60% of the total cases of gastric cancer in the world), with an estimated 50,000 gastric cancer-related deaths per year in Japan (3). The estimated number of gastric cancer cases in Europe in 2018 was 133,100 (3.4%) with 102,200 estimated deaths (4).

Half of gastric cancer cases are diagnosed at an advanced and metastatic stage, this is due to its late onset and nonspecific symptoms; the most common sites of metastases are the liver, peritoneal surface and distant lymph nodes (5). There are two types of gastric cancer liver metastases (GCLM): synchronous metastases, occurring before surgery or within 180 days after gastrectomy, and metachronous metastases, which appears at least 6 months after gastrectomy (6-8). Synchronous GCLM is detected in approximately 3.5% to 14% of gastric cancer cases and about 37% of patients undergoing 'curative' gastrectomy develop metachronous hepatic metastases (9). Over the past three decades, the management of liver metastases from colorectal cancer has markedly advanced and the role of surgical treatment has been well established. Just 30 years ago, 3- and 5-year survival rates for patients with stage I disease were 12% and 20%, respectively (10); currently, the 10-year survival rate is 24%, with an observed 20% cure rate (11). Liver involvement from gastric cancer is often characterized by multiple bilobar intrahepatic nodules; moreover, in many cases, extrahepatic disease can coexist, including extensive lymph node metastases, peritoneal seeding and direct tumor invasion of other organs (12).

Chemotherapy is considered the gold standard treatment of patients with metastatic gastric cancer and the role of surgery is controversial and still debated. However, some studies have demonstrated that hepatic resection for GCLM has a favorable impact on overall survival (13-15).

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Key Words: Gastric cancer, metachronous liver metastasis, liver resection, review.

The aim of our study was to examine the literature analyzing data of patients with metachronous GCLM in an effort to evaluate the role of hepatic resection for metachronous GCLM, also comparing the 1-, 3-, 5-year survival rates with those of patients with synchronous GCLM undergoing liver resection.

Materials and Methods

Literature search strategy. An electronic literature research was conducted using PubMed, Web of Science, Cochrane Library, BMJ Clinical Evidence and UpToDate databases. The search terms: "gastric cancer" (OR "gastric carcinoma", OR "stomach cancer") AND "metachronous" AND "liver metastases" (OR "hepatic metastases"), AND "liver resection" (OR "hepatectomy") were used. The reference list of each article retrieved was analyzed to identify other relevant studies.

Study selection. Publications were included in this study when they met the following inclusion criteria: (i) Written in English, published from January 2000 to December 2020, with case studies starting from 1985; (ii) including at least five patients who underwent curative gastrectomy (R0) for primary gastric cancer, with metachronous GCLM in the absence of other disease localization, treated with surgical resection or systemic chemotherapy or local ablation technique; (iii) reporting data on 1-, 3- and 5-year overall survival. We included prospective and retrospective studies, unicentric and multicentric. Articles with the following characteristics were excluded: (i) Case reports or observational studies; (ii) reviews or metanalyses; (iii) cohort of patients with GCLM whose survival rates were not specified. In the case of articles published by the same author or analyzing the same cohort of patients, the most recent analysis was included in the study, except for that of Tiberio *et al*. (13) of which the most recent was not chosen because more relevant and comprehensive data were given in a previous report.

Data extraction and quality assessment. Two reviewers (AM and MP) independently screened the articles, evaluating title, abstract and key words, then analyzed the chosen articles and collected the following data from each study: First author, year of publication, study design, number of patients with metachronous GCLM, primary and metastatic tumor characteristics, treatment regimen and outcomes of interest as 1-,3- and 5-year overall survival rates. The senior author (PA) was involved in discussing and resolving any disagreement.

The data collected was organized following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (16). Study quality was assessed using the Newcastle Ottawa Scale, the instruments recommended by the Cochrane Collaboration in order to minimize bias risk for non-randomized studies included in systematic review (17).

Results

Characteristics of the included studies. A total of 16,008 articles were selected and evaluated from the initial search. Of these, 15,971 were excluded after the evaluation of title and abstracts. A final total of 37 articles were potentially eligible for the study. Considering the inclusion and exclusion criteria listed in the Materials and Methods, 24 articles were excluded, therefore we analyzed the data of 12 articles extracted from the literature search (7, 12-15, 18-24) and data of six articles retrieved by searching through references (6, 25-29), for a final total of 18 articles (Figure 1).

All selected studies were retrospective, no prospective or randomized trial met the inclusion criteria. Six studies were multicenter, while the rest collected patients from a single hospital. Fourteen studies included patients from Asia, and four from Europe. These included a total of 1,996 patients, ranging from 12 to 653 per study, with liver recurrence from gastric cancer, and in 1,579 cases they had metachronous metastases. The period of study started before 2000 in 11 articles and in the remaining seven from 2000 onwards.

Characteristics of the patients. Main patient characteristics are summarized in Table I. In all studies, there was a prevalence for male patients, who overall represented 77% of the total population, with a male to female ratio of 3:1. The median age of the population was 55.5 years. All patients underwent surgery for primary gastric cancer. Imaging investigations during follow up included abdominal computed tomography in all studies, while in some cases ultrasound and magnetic resonance imaging were also used as complementary examinations. The articles by Tiberio *et al*. (13), Ishida *et al*. (18), Komeda *et al*. (20), Li *et al*. (7) and Xiao *et al*. (23) included only patients with metachronous metastases, for a total of 1,186 cases, of which 129 (10.9%) underwent liver resection. These five studies presented more homogeneous data and allowed us to make a comparison of the overall survival between patients with metachronous metastases from gastric cancer undergoing chemotherapy or surgery.

The article by Komeda *et al*. (20) analyzed a pool of 24 patients that all underwent hepatic resection for liver metastases. In the remaining studies, patients were divided according to treatment. In the study by Tiberio *et al*., 73 patients were studied; of these 11 (15.1%) were treated by surgery, 17 received chemotherapy and 45 underwent palliative care (13). Xiao *et al*. collected data from 436 patients, of these 60 (13.8%) underwent surgery (considering surgery and radiofrequency ablation (RFA), 240 (55.5%) underwent transcatheter arterial chemoembolization (TACE) or microwave coagulation therapy, 92 (21%) received chemotherapy and 44 (10%) supportive therapy (23). Li *et al*. included 653 patients in their cohort: 34 (5%) underwent liver resection and 619 (95%) did not (7). Ishida *et al*. evaluated data from 15 patients with early gastric cancer, who developed metachronous GCLM and treated with liver resection (33%), chemotherapy (53%) and palliative care (14%) (18).

The histological characteristics, location and type of gastric resection performed for primary gastric cancer are shown in Table II.

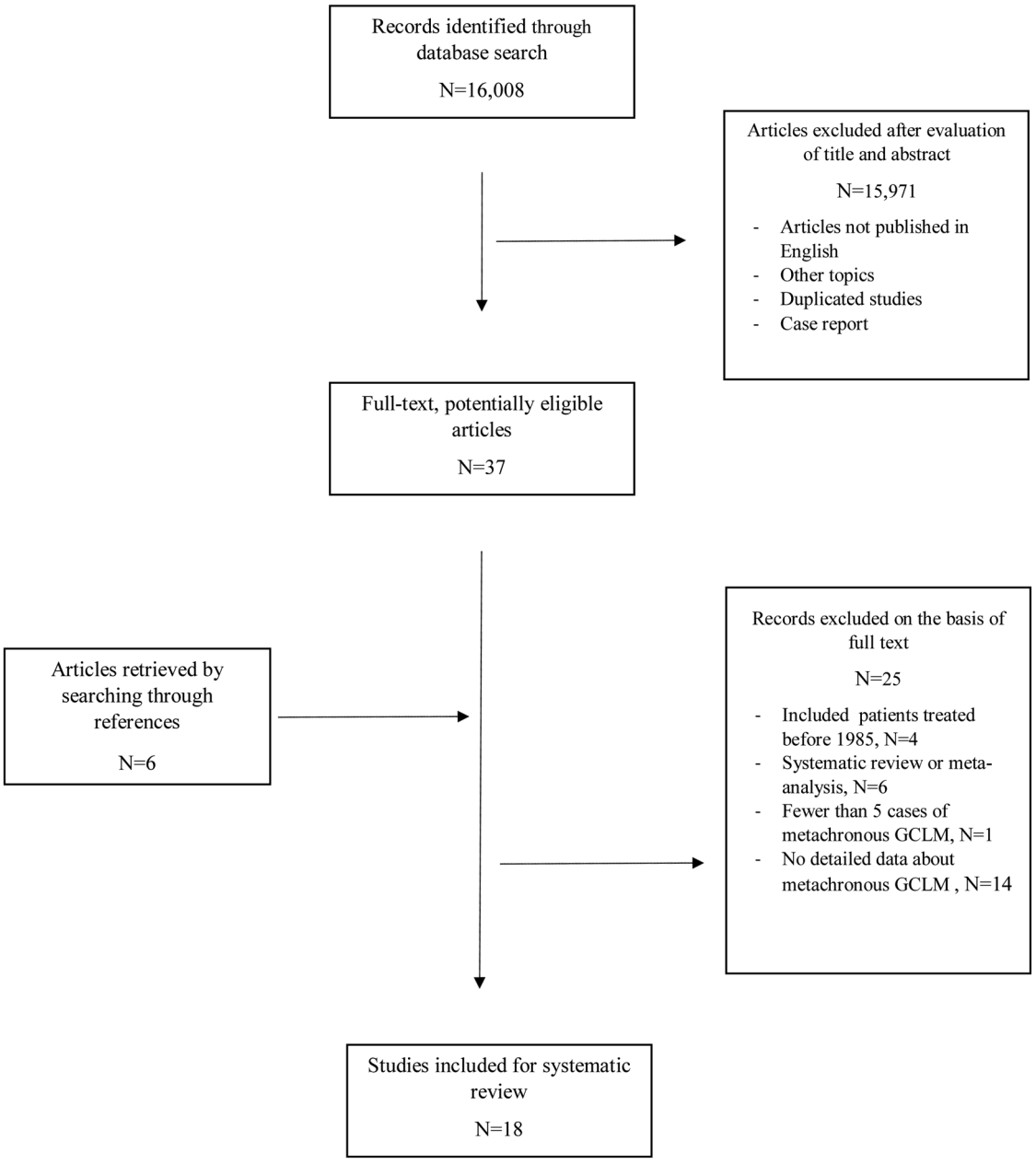

Figure 1. *Literature search strategy.*

Characteristics of GCLM and hepatic resection (Table III). Three studies reported data about timing of the appearance of metachronous GCLM, all agreed that the first 2 years represent the period in which the development of liver metastases is most likely. In Tiberio *et al*.'s study, 42 patients (57%) developed liver metastases in the first 11 months after gastrectomy, 31 (43%) after 12 months or more and of these only seven (9.6%) after 2 years (13). Xiao *et al*.'s study reported a median liver metastasis-free interval after gastrectomy of 14 months, and in 68.5% of patients, metastases were diagnosed within the first 2 years; T-stage (p=0.041), N-stage (p=0.023) and lymphovascular invasion (p<0.001) were shown to be significantly independent indicators determining the interval to metachronous GCLM (23). Li *et al*. included 653 patients in their cohort: 34 (5%) underwent liver resection and 619 (95%) did not (7). Ishida *et al*. reported the median range of time to liver metastasis detection of 12 months (18). In two studies (13, 23), the

Table I. *Patient characteristics of the retrieved studies.*

Authors (Ref)	Patients, n	Met/Syn, n	Median age (range), years	Gender (M/F)	Inclusion period	NOS
Baek *et al.* (19)	12	9/3	61 (51-74)	11/1	2003-2010	6
Garancini *et al.* (27)	21	9/12	64 (44-89)	14/7	2003-2010	5
Guner *et al.* (28)	98	59/39	60 (31-84)	78/20	1998-2013	6
Ishida *et al.* (18)	15	15/0	64 (45-72)	12/3	1991-2005	6
Kawahara *et al.* (24)	20	9/11	73.5 (53-89)	13/7	2006-2016	6
Kinoshita *et al.* (21)	256	150/106	64 (32-89)	207/49	1990-2010	6
Koga *et al.* (12)	42	22/20	64 (44-89)	30/12	1985-2005	6
Komeda *et al.* (20)	24	23/1	69.5 (42-79)	21/3	2000-2012	6
Li *et al.* (7)	653	653/0	68/62	480/173	1996-2012	6
Makino *et al.* (14)	63	32/31	66 (58-74)	51/12	1992-2007	6
Ministrini *et al.* (29)	144	32/112	68 (59.5-75)	94/50	1990-2017	5
Morise *et al.* (26)	18	7/11	64 (51-76)	16/2	1989-2004	5
Oguro *et al.* (22)	26	20/6	69.5 (49-81)	23/3	2002-2012	6
Sakamoto *et al.* (25)	37	21/16	64 (39-76)	29/8	1990-2005	6
Tatsubayashi *et al.* (15)	28	13/15	72 (39-86)	25/5	2004-2014	6
Thelen *et al.* (6)	24	9/15	64 (41-84)	17/7	1988-2002	5
Tiberio *et al.* (13)	79	73/0	66±11	52/21	1990-2004	6
Xiao *et al.* (23)	436	436/0	61 (29-85)	368/68	2001-2016	6

M: Male; F: female; Met: metachronous metastasis; NOS: Newcastle Ottawa Scale; Syn: synchronous metastasis.

Table II. *Characteristics of gastric tumor.*

Study	Patients, n	T-Status, n			N-Status, n	Histology		Location of GC		Type of GR	
		1	2-3	4		Diff	Undiff	Distal 1/3	Proximal 2/3	Partial	Total
Ishida *et al.* (18)	15	15	0	0	N+: 7 N–: 8	7	8	2	13	14	1
Komeda *et al.* (20)	24	0	24	0	N+: 14 N–: 10	22	2	11	13	15	9
Li *et al.* (7)	653		n.a.		n.a.	n.a.		n.a		n.a.	
Tiberio *et al.* (13)	73	3*	72*	7*	N+: 66 N–: 7	36	37	n.a		n.a	
Xiao *et al.* (23)	436	48	80	244	N0-2: 340 N3: 96	140	232	236	200	n.a.	

Diff: Differentiated; GC: gastric cancer; GR: gastric resection.; M: metastasis; N: nodes; n.a.: not available; T: tumor; Undiff: undifferentiated. *Data faithfully reported from the article.

extent of hepatic recurrence was classified according to the Japanese Research Society for Gastric Cancer. In the study by Tiberio *et al.*, the extent of liver metastasis (H) was H1 in 23 (31.5%) cases, H2 in 17 (23.3%) cases and H3 in 33 (45.2%) cases (13); H3 patients have always been considered ineligible for surgery. A total of 11 (15%) patients were treated with surgery: in eight cases there was only one metastasis, in the remaining three cases there were two (13). Surgical procedures performed were five non-anatomical resections, three segmentectomies, two bi-segmentectomies and one right hepatectomy (13). Patients studied by Xiao *et al.* were classified as follows: 176 (40.4%) H1, 120 (27.5%) H2 and 140 (32.1%) H3. Fifty-two (87%) H1 patients underwent surgical resection and eight (13%) H2; also in this case series no H3 patients underwent surgical resection (23). The diameter of the major metastasis was ≤3 cm in 184 cases, >3 cm in 188 cases. Komeda *et al.* reported data on 24 cases of metachronous GCLM, 17 (71%) of which were solitary and seven (29%) multiple, with lesions in 17 (71%) cases being ≤5 cm and >5 cm in seven (29%) cases; liver resection was anatomical in 15 cases, and not anatomical in nine cases (20).

Survival outcomes (Table IV). In the five works analyzed there was an increase in the survival rate of patients treated (with surgery, chemotherapy or local ablative technique)

Table III. *Characteristic of gastric cancer liver metastasis (LM).*

Study	Patients, n	Liver recurrence, n		Extent of LM, n			Size of LM, n	Surgical resection, %	Type of hepatectomy		Post-surgery mortality		Post-surgery morbidity	
		<2 Years	≥2 Years	H1	H2	H3			Minor	Major	Yes	No	Yes	No
Ishida *et al*. (18)	15	n.a.	n.a.	n.a	n.a.	n.a.	n.a.	5	n.a.		0	5	n.a.	
Komeda *et al*. (20)	24	n.a.	n.a.	n.a.	n.a.	n.a.	≤5 cm: 17 >5 cm: 7	24	10	n.a.	0	24	11	13
Li *et al*. (7)	653	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	34	n.a.		n.a.		n.a.	
Tiberio *et al*. (13)	73	66	7	23	17	33	n.a.	11	10	1	0	11	0	11
Xiao *et al*. (23)	436	298	138	176	120	140	≤3 cm: 184 >3 cm: 188	60	n.a.		n.a.		n.a.	

Table IV. *Survival outcomes of patients with gastric cancer liver metastasis.*

	After surgery, %					After chemotherapy, %					
Study	n	Median	1 Year	3 Years	5 Years	n	Median	1 Year	3 Years	5 Years	*p*-Value
Ishida *et al*. (18)	5	-	-	-	18	8	-	-	-	-	-
Komeda *et al*. (20)	23	22.3	78.3	40.1	40.1	-	-	-	-	-	-
Li *et al*. (7)	34	26.16	73.5	36.9	24.5	619	3.13	24.5	9.1	6.6	<0.001
Tiberio *et al*. (13)	11	-	81	20	20	9	-	33	-	-	<0.0001
Xiao *et al*. (23)	60	25	84	46	28	92	11	32	-	-	<0.001

compared to those prescribed palliative care; in addition, an increase in the survival of selected patients (*i.e*., without extrahepatic non-curative factors and feasible complete macroscopic removal of liver deposits) who underwent hepatic resection compared to other treatments was reported. Komeda *et al*. (20) described a median survival of 22.3 (range=3.3-99.7) months for their cohort, with 1-, 3- and 5-year overall survival rates of 78.3%, 40.1% and 40.1%, respectively, for patients in whom curative hepatic resections were performed. In the study of Tiberio *et al*., overall survival from the diagnosis of liver recurrence was 33%, 10%, 6% and 4% at 1, 2, 3 and 5 years, respectively, with a median survival of 7 (range=1-91) months. Their multivariate analysis showed that the therapeutic approach to metastases increased survival, in particular when surgical resection was performed ($p<0.001$); median survival of non-treated patients was 5 months, increasing to 12 when chemotherapy was employed and 23 months after surgery (13). Li *et al*. reported that overall survival was significantly better for the group of patients that underwent liver resection than for those treated with chemotherapy (median overall survival=26.16 *vs*. 3.13 months, respectively) (7), even after the introduction of the XELOX protocol (30). Xiao *et al*.'s work showed a median survival time of 25, 15 and 11 months for patients treated with surgery, TACE and systemic chemotherapy, respectively (23). Ishida *et al*. found that the 5-year survival rate after curative resection was 18.8% (18).

Prognostic factors. Among the prognostic factors, elements related to both the primary neoplasm and liver metastases were described. For Xiao and colleagues, (23) N-stage, extent of liver metastases (H) and hepatic surgical treatment were independent prognostic survival factors after the appearance of GCLM The study of Tiberio *et al*. showed that the T-stage, N-stage and grade of primary neoplasm, as well as the therapeutic approach to metastases were independent prognostic survival factors. In particular, patients with N+ disease (regardless of the extent of lymph node involvement, N1-N3) had a worse prognosis. The therapeutic approach to liver recurrence demonstrated the strongest association with survival, in particular when hepatic resection was performed ($p<0.001$) (13). Komeda *et al*. identified the maximum size of GCLM (>5 cm) as the only significant independent predictor of poor prognosis for overall survival, a maximum metastasis size ≤5 cm was identified as a good indicator for surgery (20). Ishida *et al*. reported submucosal invasion and lymphovascular involvement to be independent risk factors for the development of GCLM ($p<0.001$) (18).

Synchronous vs. metachronous GCLM (Table V). We analyzed the data for 1-,3 and 5-year survival of patients with

Table V. *Overall survival for patients with synchronous vs. metachronous gastric cancer liver metastasis.*

	Metachronous, %					Synchronous, %					
Study	n	Median	1 Year	3 Years	5 Years	n	Median	1 Year	3 Years	5 Years	*p*-Value
Baek *et al.* (19)	9	29	65	38	-	3	22	65	33	-	0.596
Garancini *et al.* (27)	9	-	68.3	34.9	-	12	-	56.8	28.3	-	0.115
Guner *et al.* (28)	42	24	79.1	40.6	30.0	26	24	79.1	40.6	30.0	n.a.
Ishida *et al.* (18)	5	-	-	-	18.8	-	-	-	-	-	n.a.
Kawahara *et al.* (24)	9	42	80	55.5	31.7	11	42	80	55.8	31.7	0.660
Kinoshita *et al.* (21)	150	31.1	77.3	41.9	31.1	106	31.1	77.3	41.9	31.1	0.125
Koga *et al.* (12)	22	34	78	50	40	20	22	74.0	47	47	0.77
Komeda *et al.* (20)	23	22.3	78.3	40.1	40.1	1	-	-	-	-	n.a
Li *et al.* (7)	34	26.16	73.5	36.9	24.5	-	-	-	-	-	n.a.
Makino *et al.* (14)	7	31.2	85.7	34.3	34.3	9	49.9	77.8	55.6	37.0	0.9
Ministrini *et al.* (29)	32	31.0	-	-	-	109	11.2	-	-	-	0.004
Morise *et al.* (26)	7	-	80	30	-	11	-	45.5	27.3	27.3	0.37
Oguro *et al.* (22)	20	-	73.7	46.4	18.5	6	-	62.5	20	-	0.06
Sakamoto *et al.* (25)	21	31	-	-	9	16	30	-	-	15	n.a.
Tatsubayashi *et al.* (15)	13	-	100	77.7	59	15	-	84	40	13	0.017
Thelen *et al.* (6)	9	17	-	-	-	15	5	-	-	0	n.a.
Tiberio *et al.* (13)	11	-	81	20	20	-	-	-	-	0	n.a.
Xiao *et al.* (23)	60	25	84	46	28	-	-	-	-	-	n.a.

synchronous or metachronous GCLM who underwent liver resection. Two studies reported a significantly longer survival for patients undergoing liver resection for metachronous GCLM compared to patients with synchronous metastases (15, 27). Tatsubayashi *et al.* also noted that postoperative complications were more common in patients with synchronous GCLM (p=0.002) and that the length of hospital stay was significantly prolonged (p=0.003) (15).

Discussion

Patients who develop GCLM have poor survival rates, despite developments in diagnostics and therapeutic possibilities (2). Nowadays, the recommended treatments in patients with GCLM are chemotherapy alone, upfront surgery or neoadjuvant chemotherapy and, subsequently, surgery (31). According to the European Society for Medical Oncology Guidelines, patients with oligometastatic gastric cancer (stage IV) have no indication for surgical treatment, only for chemotherapy (32). These indications are supported by a randomized trial that did not demonstrate an increase in survival in patients with oligometastatic stomach cancer who underwent surgery (33). On the contrary, the Japanese Guidelines recommend surgical resection only for cases with "a small number of metastases" with no other incurable factor (34). In the literature, we found retrospective studies that support surgical resection as a valid therapeutic option for patients with GCLM. In a retrospective multicenter study, Makino *et al.* assessed the overall survival rates of patients with GCLM treated with surgical resection or chemotherapy; surgically treated patients had 1-, 3- and 5-year survival of 87.5%, 56.3%, 42.2% compared to 53.2%, 4.2% and 0% for patients who underwent chemotherapy (p<0.0001) (14). Similar results were also found by other studies (7, 23). Kataoka *et al.* sent a questionnaire to the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Group and the Japan Clinical Oncology Group Stomach Cancer Study Group to investigate how they manage patients with GCLM (31). The survey showed that in cases of metachronous GCLM, the most used treatment was preoperative chemotherapy followed by liver resection; in Europe, 33.3% chose preoperative chemotherapy followed by surgery, while 30.3% preferred to treat metastases with chemotherapy alone and 36% choose other treatments (RFA alone or with chemotherapy) (31).

The role of surgery for patients with GCLM is controversial. The number of studies on this topic is increasing, although they are based on retrospective data and limited case series (31). Analyzing the various articles, we noted that there were no definite prognostic factors. From the statistical analyses of the different groups of patients, different prognostic factors were found to be statistically significant in different studies. Xiao *et al.* found that N-stage, H type and treatment of metachronous GCLM were statistically significant prognostic factors (p<0.05) on multivariate analysis (23). Similar results were found by Tiberio *et al.* (13). From the statistical analyses of Li *et al.*, it emerged that liver resection increased the overall survival

of patients with metachronous GCLM (7). Among the studies that did not show survival differences between patients with synchronous or metachronous GCLM, the presence of a solitary metastasis and a size <5 cm were found to be statistically significant prognostic factors of overall survival ($p<0.05$) (14, 24, 25, 27).

We also highlight the lack of data in the literature on patients with metachronous GCLM, probably due to the difficulty in finding patients with potential surgical indication. Gastric cancer in fact has an aggressive biological behavior and it is very common to identify the presence of liver metastases together with other localizations of disease at diagnosis (13). This lack of data made it difficult to enroll patients in case series in which the results in terms of overall survival and recurrence could be compared between patients treated with chemotherapy and those undergoing surgical resection (31). A minority of the studies included in the review selectively analyzed the survival rates and characteristics of metachronous GCLM (7, 13, 18, 20, 23). The lack of precise data and the absence of a univocal assessment of prognosis, make it difficult to select which patients can benefit from surgery. In contrast, there are a lot of data collected about patients with liver metastases from colorectal cancer and this has made it possible to draw up guidelines, supported by scientific evidence, regarding the indications for surgery, with an improvement in the overall survival of patients undergoing liver resection. Furthermore, Fukuchi *et al*. found that patients with an initial unresectable gastric tumor may benefit from conversion therapy, after a response to both first- and second-line chemotherapy, with a survival benefit (35, 36). To our knowledge, there are no studies that consider conversion therapy in the treatment of patients with GCLM, but in the future this might be one of the therapeutic possibilities for patients who develop GCLM. It The need for clinical trials and studies including an adequate number of patients with GCLM undergoing liver resection is therefore evident, to establish significant prognostic factors and define the indications for surgical treatment of GCLM. Surgical treatment must in fact be reserved for those cases that have shown an improvement in prognosis compared to other treatments (chemotherapy, TACE, RFA *etc*.).

In conclusion, it is not yet clear what the optimal treatment of metachronous GCLM without further localization of disease should be. Several studies suggest that these patients should not be referred for palliative care but treated with a multimodal 'aggressive' approach, including surgical resection, chemotherapy and local ablation therapy. Our review shows that in selected cases, such as those with H1 and H2 liver involvement, and in particular when metastases are less than 5 cm in size, surgery may play a role in increasing the survival rate. Surprisingly all authors agreed with these results. On the other hand, it is clear that for H3 patients, surgery is not recommended. However, data are still too few, and are from exclusively retrospective studies, with in most cases including patients with synchronous metastases. For this reason, we believe that prospective studies that include only patients who develop metachronous GCLM can help in choosing the optimal treatment for this stage of disease.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

PA and GR approved the final version to be published, MP and AM conceived, designed and wrote the study, FDA: provided data, GN collected data, LA and SV analysed data, NP critically revised the article.

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