Gastric cancer and brain metastasis: A systematic review and meta-analysis

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Abstract. Gastric cancer (GC) constitutes one of the most wide-ranging cancers, with brain metastasis (BM) being a markedly uncommon and unfavorable outcome. The present meta-analysis evaluated the relationship between no-surgical treatment vs. additional surgical BM resection on the patient's quality of life and potential survival using electronic databases, including PubMed (1980-April 2024), Medline (1980-April 2024), Cochrane Library, and EMBASE (1980-April 2024). After a literature search, six articles were included in the final study pool. The number of patients with BM and conservative treatment was 289 (80.05%) compared with those that underwent an additional surgical resection 72 (19.95%). The mean age was 59.2 years, and the males were 195 (73.8%) of 264 available from five studies. The findings of the present meta-analysis revealed that the curative effect of BM tumor resection on patients with GC undergoing additional treatment with stereotactic radiosurgery, whole-brain radiotherapy or chemotherapy was favorable for their survival.

Introduction

Gastric cancer (GC) constitutes one of the most wide-ranging cancers, with >1 million affected patients each year (1), and usually recurs as metastasis to the liver and peritoneum (2). However, brain metastasis (BM) is very uncommon (<1%), and the prognosis is markedly unfavorable compared with CG metastasis to other organs, with a median survival at this stage of the cancer approximately 2 to 4 months (3).

Due to the relative rarity of the disease, a significant number of patients with GC quickly succumb to the disease after receiving a diagnosis of BM, or BM is identified after death in numerous autopsies (4). In addition, there are relatively few studies with GC and developed BM, and management options such as stereotactic radiosurgery (SRS) or chemotherapy, whole-brain radiotherapy (WBRT), and surgical resection are still under examination (5).

In this respect, the present meta-analysis assessed the relationship between no-surgical treatment (SRS, WBRT or chemotherapy) vs. the additional microsurgical BM resection in terms of the patient's quality of life and potential survival advantage.

Materials and methods

Literature search strategy. The meta-analysis investigated studies that compared no-surgical treatments (SRS, WBRT or chemotherapy) with studies that involved surgery for BM resection. The studies were found in electronic databases such as PubMed (https://www.ncbi.nlm.nih.gov/pmc/?db=PMC) (1980-April 2024), Medline (https://www.nlm.nih.gov/medline/medline_home.html) (1980-April 2024), Cochrane Library (https://library.udel.edu/databases/cochrane/), and EMBASE (https://libguides.lib.cuhk.edu.hk/medicine/database/embase) (1980-April 2024). A protocol and documentation plan was created by applying the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (6). The following key words were used for the search: 'Gastric cancer', 'brain metastasis', and 'gastric cancer and brain metastasis'.

Inclusion and exclusion criteria. The current meta-analysis assembled the PICOS parameters from the included studies (7).

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Inclusion of studies was based on the following: i) The population was limited to patients with GC and BM; ii) An additional surgical intervention for BM was implemented; iii) survival outcomes were compared and analyzed; and iv) the overall survival of GC patients with BM who received additional surgical management was quantified. In order to mitigate publication bias, the ultimate goal was to gather a uniform set of studies that solely assessed two modalities: A comparison between no-surgical treatments such as SRS, WBRT or chemotherapy, and an additional surgical BM resection for patients with GC.

All the articles that were case reports, reviews, editorials, and not in English were excluded. Articles with pediatric populations, novel procedures in the investigational phase, those that included only one of the two management options, and those that disclosed doubtful results were also excluded. Two investigators (GF, a neurosurgeon and GC, a gastric cancer surgeon) individually extracted information from the enclosed articles using the epidemiology principles of meta-analysis. In cases of disagreement, the decision of an additional author was considered. The post-interventional outcomes stated in the last collection of articles were evaluated at least 6 months following surgical treatment (surgical resection of BM in patients with GC). In addition, to reduce the risk of bias in the included articles, a quality assessment tool (the Newcastle-Ottawa Scale) was used (Table I) (8). All patients with GC were divided into two groups: Those with no-surgical treatment (SRS, WBRT or chemotherapy) and those with an additional surgical BM resection.

Statistical analysis. All data were evaluated via Review Manager Software (RevMan), version 5.4 (https://www.risetku.com/blog/revman). I^2 statistics assessed heterogeneity among studies. A meta-analysis was evaluated using a random-effect model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics. Following the prime literature search, 42 studies were suitable for additional investigation. When all the criteria were applied, six articles were included in the final study pool (Fig. 1) (5,9-13). The entire data of these studies are presented in Table II. The total sample of patients collected from these six articles with GC was 32.372, and from these patients 361 (1.1%) were identified with BM. The number of patients with BM and no-surgical treatment was 289 (80.1%) compared with those that underwent an additional surgical resection which was 72 (19.9%). The mean age of the patients was 59.2 years, and the males were 195 (73.9%) of the 264 available from five studies (5,9-12) (Table II).

Survival >6 months. Data was gathered from six articles (5,9-13). In the entire group of patients with GC and BM, there were 76 out of the 361 (21.1%) patients [39 of 289 (13.5%) in the no-surgical treatment group, and 37 out of the 72 (51.4%) with an additional surgical BM resection], showing a statistically significant difference between the groups (OR, 4.63; 95% CI, 2.52 to 8.52; $P<0.05$) with no heterogeneity ($P=0.96$ and $I^2=0\%$) (Fig. 2 and Table III), and thus the superiority of the additional surgical BM resection group compared with no-surgical treatment group; Fig. 2) (Table III). When studying the funnel plot of the same parameter, it was observed that the study results showed no publication bias (Fig. 3).

Discussion

Prognosis of patients with BM from GC. BM constitutes ~13% of all brain tumors, with the primary malignancy mostly found in the lung and secondarily in the breast (14). Considering that BM from GC is extremely rare and usually occurs hematogenously with a markedly unfavorable outcome, the present meta-analysis revealed that additional surgical treatment of BM was associated with an improved prognosis (survival, >6 months) than no-surgical management (SRS, WBRT or chemotherapy). It was determined that in the entire group of patients with GC and BM, there were 51.4% of patients with an additional surgical BM resection compared with 13.5% in those with no-surgical treatment, which had improved outcomes (survival, >6 months).

Frequency of BM and GC. BM accounts for ~13% of central nervous system (CNS) tumors and mainly originates from melanoma, chorioepitheliomas and lung cancer (14). On the other hand, GC is the 5th most frequent tumor metastasizing to various organs, with markedly unfavorable outcomes (15). BM in patients with GC is relatively rare (0.5-0.7%), and in most cases, the diagnosis occurs at a late stage, which may signify that the survival of those patients is markedly short (16). In the present meta-analysis, BM was identified in 1.1% of the total number of patients with GC.

Conversion therapy of GC with BM and survival. The main approach for managing GC according to literature is palliative chemotherapy (17). On the other hand, conversion therapy, an expansion of exchange chemotherapy, aids in achieving surgical resection of a primary tumor that was initially considered to be technically difficult to approach or inoperable, encompassing the utililization of radiotherapy, chemotherapy, or target therapy for a locally advanced tumor. In terms of palliative management, conversion therapy can result in extended survival times and improved outcomes for patients with metastatic GC (18).

Surgical resection as the sole treatment for the primary tumor of GC with BM and survival. As only 10% of patients with metastatic GC underwent surgical removal, surgical procedures on the primary tumor mostly improved the outcome of these patients (5). Conversely, compared with patients with BM, patients with GC with lung and liver metastases exhibited an improved prognosis (5). In addition, the location and the number of BMs also influenced the outcome of patients with GC. Thus, the prognosis of metastatic GC is not easy to detect, and the resection alone of the primary tumor may be better when it includes a BM site. The meta-analysis showed that an additional surgical removal of BM is related to favorable outcomes.

Prognosis in patients with GC and BM. A median age of >65 years old, signet ring cell carcinoma histological type, and the IV stage of GC constitute some of the main parameters related to unfavorable outcomes and low patient survival with GC and BM (19). According to the literature, the prognosis of patients with metastatic GC depends on the metastatic location,

Table I. Newcastle-Ottawa scale quality assessment of the final article pool.

First author, year	Study design	Newcastle-Ottawa scale				(Refs.)
		Selection	Comparability	Exposure	Total scores	
York *et al*, 1999	One single center, retrospective	3	3	3	9	(5)
Kasakura *et al*, 2000	One single center, retrospective	3	2	2	7	(9)
Qiu *et al*, 2018	Multicenter, retrospective	3	3	3	9	(10)
Li *et al*, 2020	Multicenter, retrospective	3	2	2	7	(11)
Ishizuka *et al*, 2023	One single center, retrospective	3	2	2	7	(12)
Baccili Cury Megid *et al*, 2024	One single center, retrospective	3	3	3	9	(13)

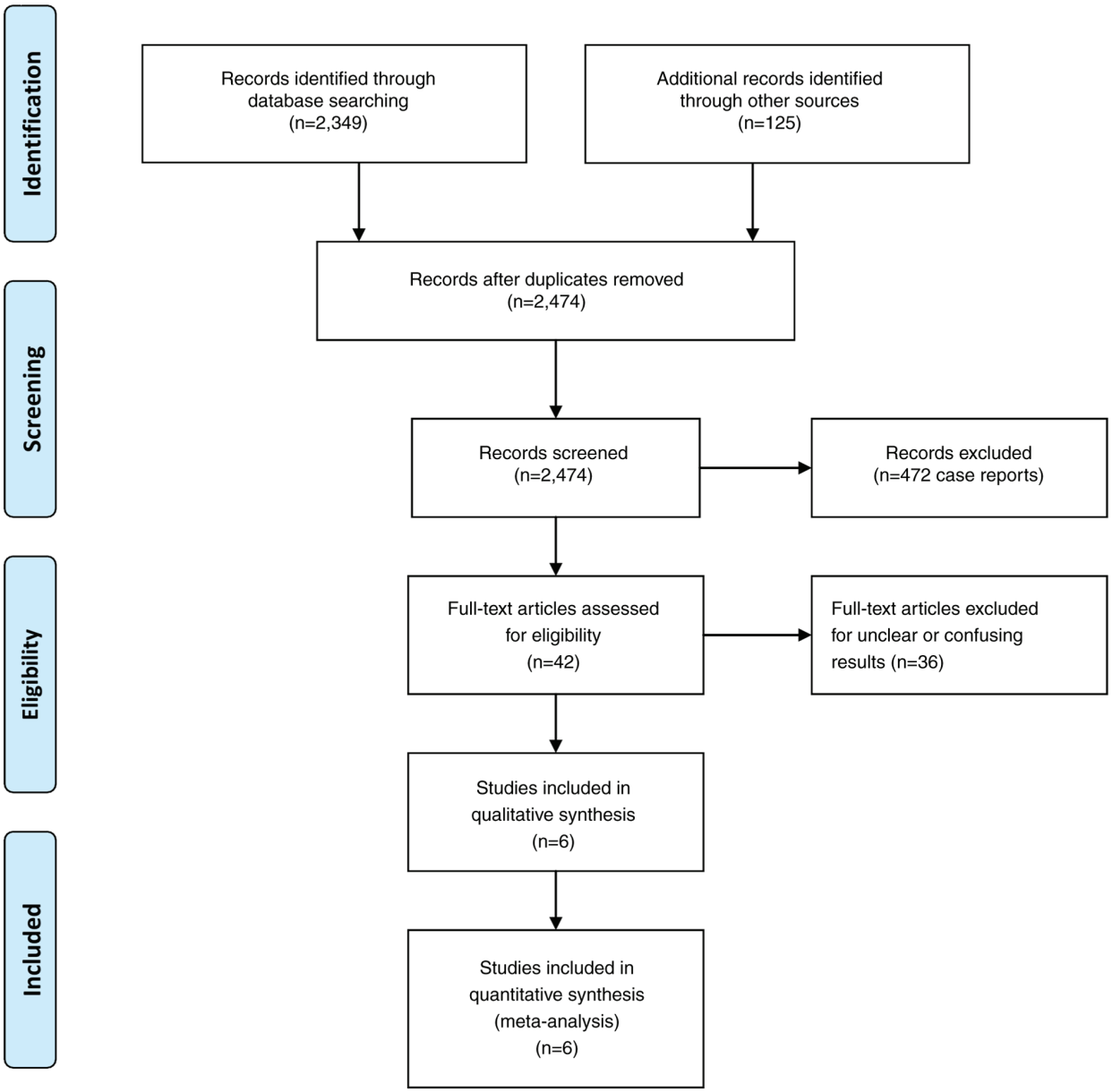

Figure 1. Flow chart of identification and eligibility of articles.

with the most unfavorable outcome in those patients with BM compared with metastasis in the lung and liver (20,21). In addition, the number and site of the metastatic lesions in the brain could also influence the survival of patients (5). New therapeutic protocols and the development of imaging equipment have led to early detection of patients with GC and BM, ultimately

Table II. Design and baseline characteristics of the included study trials.

First author, year	Sample size				Mean age of patients with BM (years)	No. of male patients with BM	Follow-up (years)	Stage of advanced cancer	Location of BM	Time from GC to BM (months)	>6-month survival		(Refs.)
	Total no. of patients with GC	Total no. of patients with GC and BM	BM no-surgical treatment	BM plus surgical treatment							BM no-surgical Treatment	BM plus Surgical Treatment	
York *et al*, 1999	3,320	24	14	10	53	18	40	III or more	14 supratentorial, 3 infratentorial, 7 multiple	9 (1-23)	5	6	(5)
Kasakura *et al*, 2000	2,322	11	8	3	54.6	9	18	III or more	7 multiple, 4 solitary supratentorial	9.6 (0.1-43.7)	1	2	(9)
Qiu *et al*, 2018	19,022	151	139	12	61.3	113	5	NR	99 multiple, 52 solitary supratentorial	NR	4	2	(10)
Li *et al*, 2020	4,221	59	41	18	51.1	44	2	NR	12 multiple, 47 solitary supratentorial	NR	12	12	(11)
Ishizuka *et al*, 2023	1,257	16	12	4	71	11	10	II or III	12 multiple, 7 solitary supratentorial	12.9	2	2	(12)
Baccili Cury Megid *et al*, 2024	2,230	100	75	25	64.4	NR	14	III or more	NR	6.7 (3,4-13,8)	15	13	(13)
Summary	32.372	361	289 (80.1%)	72 (19.9%)	59.2	195 of 264 (73.9%)	-	-	-	-	39 of 289 (13.5%)	37 of 72 (51.4%)	-

GC, gastric cancer; BM, brain metastasis; NR, not reported.

Table III. The outcome results of the meta-analysis.

		Groups				Overall effect			Heterogeneity	
Parameters	No. of studies	Total no. of patients with BM and no-surgical treatment	Total no. of patients with BM plus surgical treatment	>6-month survival of patients with BM and no-surgical treatment	>6-month survival of patients with BM plus surgical treatment	Effect estimate	95% CI	P-value	I^2 (%)	P-value
>6-month survival	6	289	72	39	37	4.63	(2.52-8.52)	<0.05	0	0.96

BM, brain metastasis; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

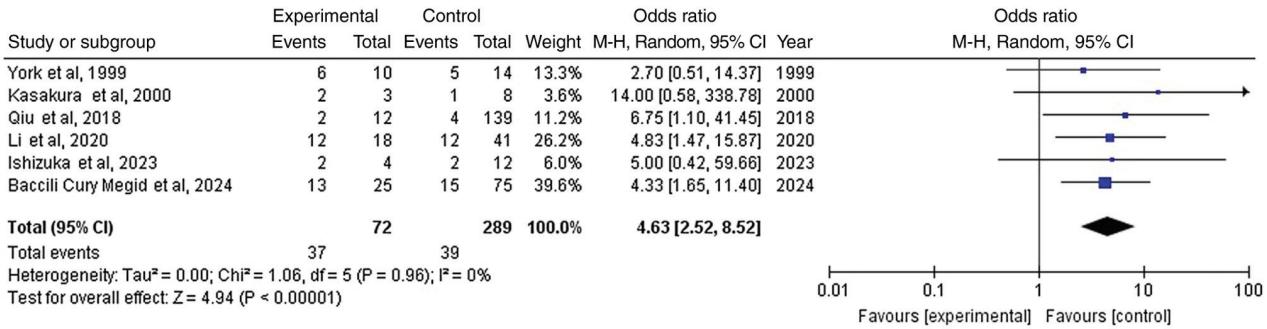

Figure 2. Forest plot of the >6-month survival. The results exhibited a statistically significant difference [(OR, 4.63; 95% CI, 2.52-8.52) and P<0.05] without heterogeneity (P=0.96 and I^2=0%). I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance; CI, confidence interval.

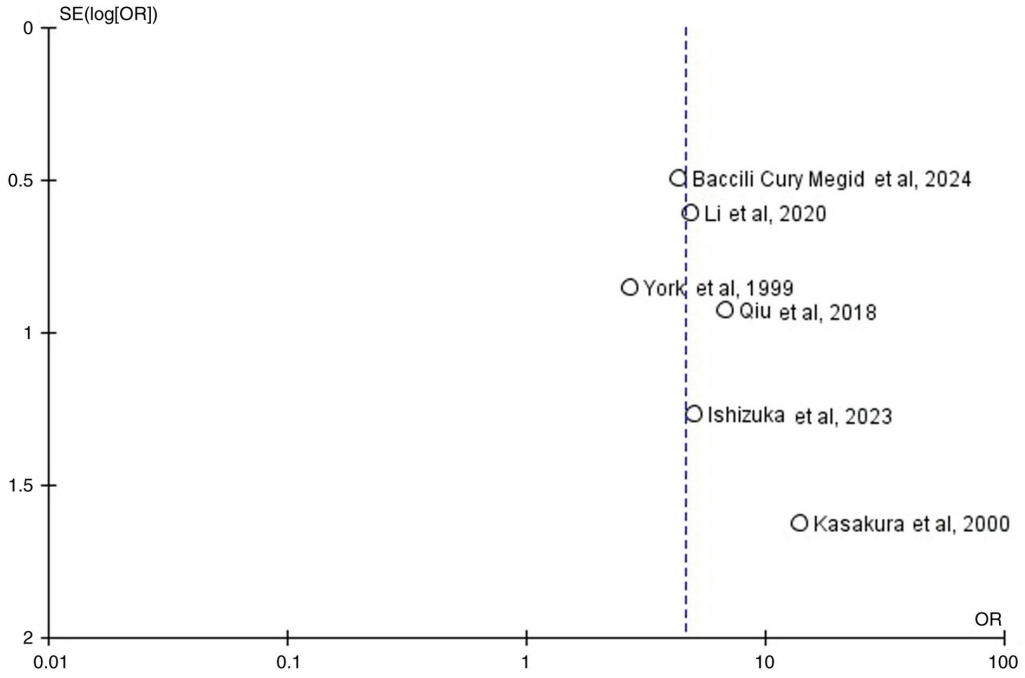

Figure 3. Funnel plot of the >6-month survival between groups, without heterogeneity (P=0.96 and I^2=0%), and thus with no publication bias. OR, odds ratio.

improving the quality of life of these patients (22). In addition, surgical management of both the primary tumor and BM in patients with GC, in combination with chemotherapy, SRS or WBRT, has extended the survival time of this fatal disease (18). The present meta-analysis revealed that the additional surgical treatment of BM compared with no-surgical management (SRS,

WBRT or chemotherapy) achieved a >6-month survival in 21.1% of patients with GC and BM.

Limitation. A limitation of the present study is that the meta-analysis pool consisted of relatively small sample sizes; consequently, the results require further validation with a large-scale sample size.

Conclusion of the findings. The findings of the present meta-analysis revealed that the curative effect of BM tumor resection on patients with GC compared with additional no-surgical treatment using SRS, WBRT or chemotherapy was favorable for their survival. However, further studies on carefully selected patients are necessary to confirm these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

GF and NF conceptualized the present study. VEG, DAS, GC, PS, KP, NT, GF and NF evaluated the data and wrote and prepared the draft of the manuscript. NF and GF applied critical revisions. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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