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REVIEW ARTICLE

Is there a role for treatment-oriented surgery in stage IV gastric cancer? A systematic review

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Abstract

To analyze the available evidence on the role of treatment-oriented surgery in stage IV gastric cancer (metastatic disease), a systematic literature search was undertaken using Medline, Embase, Cochrane, and Web-of-Science libraries. The search was not restricted to articles published within a given year range. Articles written in English language (or with abstracts written in English) were considered. All references in the chosen articles were further screened to find additional relevant publications. Both clinical series and literature reviews were included. Stage IV gastric cancer is classified into four subcategories: positive peritoneal cytology without clear macroscopic peritoneal involvement (surgery is usually performed in these cases); gross appearance peritoneal carcinomatosis [surgery, eventually with hyperthermic intraoperative peritoneal chemotherapy (HIPEC) may be considered in very selected cases with limited PCI]; nodal metastases outside the loco-regional nodes (surgery may not be denied for metastatic nodes in stations 13 and 16); and hematogenous metastases (surgery should be performed in selected cases with liver metastases suitable to R0 resection). The analysis incorporated the new biological classification of stage IV gastric cancer recently proposed by Japanese researchers (Yoshida et al. in Gastric Cancer 19:329–338. https://doi.org/10.1007/s10120-015-0575-z, 2015) into the four aforementioned subcategories to make the comparison of the issues discussed meaningful. The take home message from the existing literature is that treatment-oriented surgery may be performed in a significant proportion of patients with stage IV gastric cancer.

Keywords Gastric cancer · Stomach · Staging · TNM · Metastases · Nodal involvement · Peritoneum · Carcinomatosis

Introduction

The latest version of the UICC TNM (8th TNM Edition, 2017) defines stage IV gastric cancer as metastatic disease [2]. As such, it has been typically considered a non-surgical disease, except when surgical palliation should be performed, because it is not possible to provide relief from symptoms by means of non-surgical techniques, such as endoscopic stenting, intra-arterial embolization, and parenteral nutrition. Therefore, stage IV gastric cancer patients represent a subgroup of patients with poor prognosis, with surgical treatment being usually limited and not treatment-oriented.

However, in daily clinical practice, a number of patients with stage IV gastric cancer receive surgical treatment, sometimes with curative intent and, although in rare cases, they gain surprisingly high long-term survival rates. This article discusses the recent literature on this subject and highlights the yet unsolved clinical issues.

Materials and methods

Search methods

A systematic literature search was performed using Medline, Embase, Cochrane, and Web-of-Science libraries. The search was not restricted to a given year range. The following terms were searched separately: gastric cancer, metastases,

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stage IV, peritoneal carcinomatosis, para-aortic nodes, and peritoneal cytology. The inclusion criterion encompassed articles published in English language or with abstracts written in English from articles published in other languages. All references in the selected articles were further screened to find additional relevant publications. Articles were retrieved according to the Preferred Items for Reporting of Systematic Reviews and Meta-analyses guidelines [3] (Fig. 1).

Study selection

Articles were selected if their abstracts contained data referring to morbidity–mortality and survival rates after surgical treatment of stage IV gastric cancer. Both clinical series and literature reviews were included. Papers reporting only clinical and pathological classifications, genetic characteristics or proteomic assessment in gastric cancer, studies of risk factors for recurrence after radical treatment of non-metastatic gastric cancer, congress presentations, and letters to the editor were excluded.

Data extraction

For all eligible studies, a standard data extraction form was filled in and the following data were extracted: study design, number of patients, timing of metastases (synchronous vs metachronous), clinical presentation according to the following four subgroups: (1) positive cytology without macroscopic peritoneal nodules; (2) peritoneal carcinomatosis; (3) nodal metastases distant from loco-regional nodes; and (4) hematogenous metastases. Moreover, surgical complications in terms of morbidity and mortality, association with

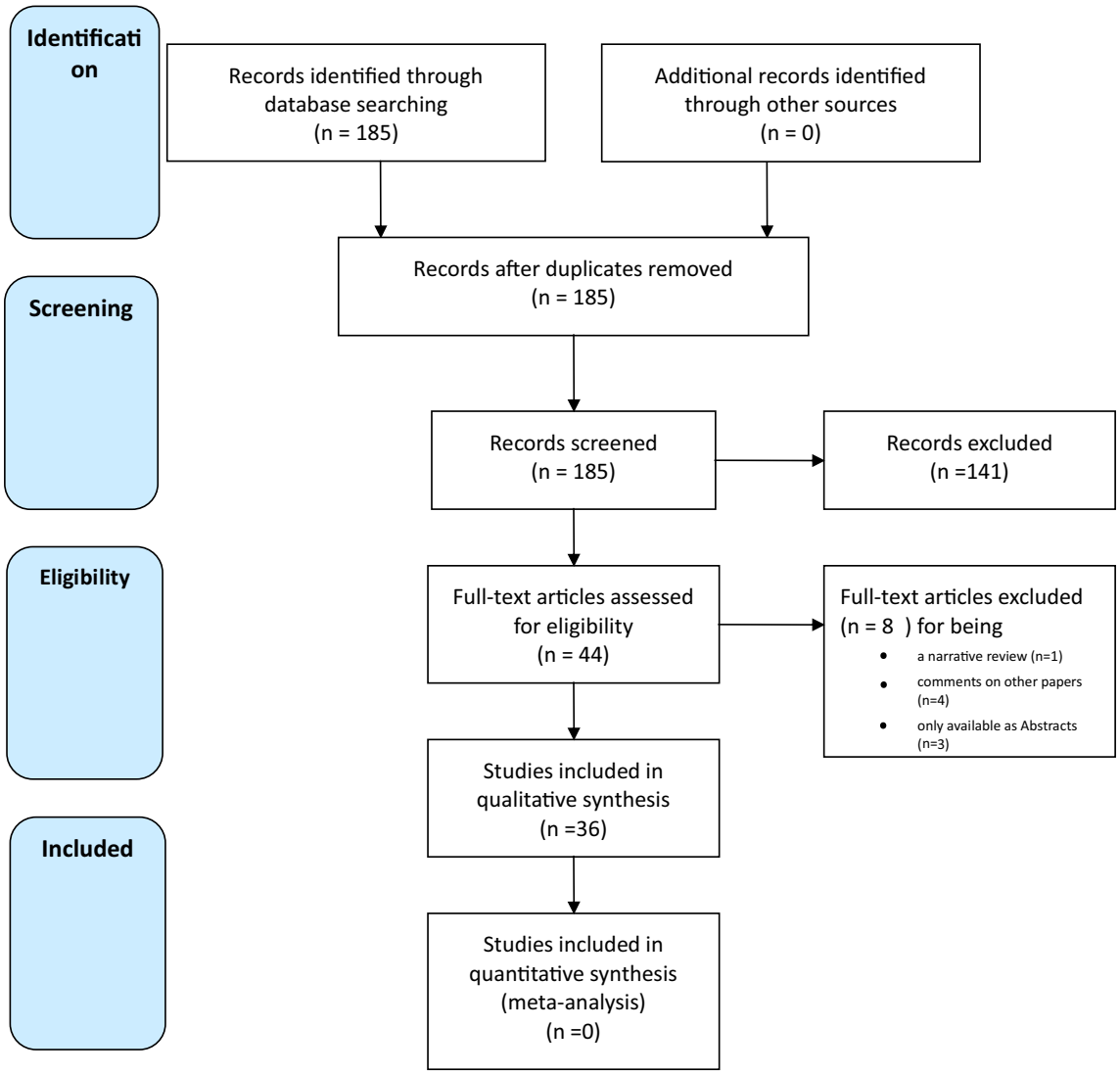

Fig. 1 Flow diagram of the literature search process (according to Preferred Reporting Items for Systematic Reviews and Meta-analyses—PRISMA 2009)

chemo and/or radiation therapy, data on survival (overall and recurrence-free survival, expressed as mean survival in months and/or 1, 2, 3, or 5-year survival rates) were collected. For statistical analysis, it was considered significant $p < 0.05$, when published. The study incorporated the new biological classification of stage IV gastric cancer recently proposed by Japanese researchers [1] into the four aforementioned subcategories to make the comparison of the issues discussed meaningful.

Results

The titles and abstracts of 185 articles were screened for eligibility independently by two authors (ZB, SM). Among these publications, 141 articles were excluded for one of the following reasons: (a) the abstract was unavailable ($n = 16$); (b) risk factors were reported for recurrence after radical surgery ($n = 26$); (c) their content was irrelevant to the topic of this study ($n = 81$); or (d) because they described other features such as the rate of metastases and their impact on survival without describing the surgical treatment of the metastases themselves ($n = 18$). These exclusion criteria left 44 articles eligible for analysis. Eight additional articles were excluded after full text examination, because they were a narrative review ($n = 1$), comments on other papers ($n = 4$), or only available as abstracts ($n = 3$). The remaining 36 articles were fully analyzed and data were extracted.

Positive cytology without macroscopic peritoneal nodules

From a number of clinical guidelines (4), harvesting peritoneal fluid for cytology is required in all cases of open or laparoscopic staging of potentially resectable gastric cancer; this is the case during pre-treatment staging and at the beginning of a planned radical gastrectomy. Cytology may be analyzed immediately, with limited sensibility, or in the subsequent days after surgery when the sensibility is to some extent better. The impact of a positive cytology on prognosis is actually unclear. On one hand, it affects the recurrence rate: in a series published in 2012 with 37 patients staged P0Cy1 after radical gastrectomy, in 100% of the cases gastric cancer did recur, and in 92% of the cases (34 pts) with peritoneal dissemination [4]. On the other hand, a number of cases with surprisingly long survival times have also been reported: in the same study [4], patients with 33-month DFS and 45-month OS were reported, while 2-year OS was reported in 45.9% of the cases. Another large series consisting of 1985 Japanese patients surgically treated for gastric cancer from 1975 to 2000 revealed that 5-year OS occurred in 15.3% of the cases and was 62.5% in the subgroup of patients without nodal involvement [5]. Thus, a potentially radical surgery can be justified in patients with P0Cy1.

A recent article by Yamaguchi et al. [6] describes the possibility to treat with a surgical-oriented approach patients with minimal or microscopic peritoneal deposits. In these patients, chemotherapy might lead to a better response (in terms of disappearance of the peritoneal deposits on CT or negativization of peritoneal cytology), with a P0Cy0 after laparoscopic restaging, which makes surgical treatment feasible and delivers longer survival compared to patients treated with chemotherapy alone.

Most clearly, patients with only positive cytology who are not surgically treated, have a very poor prognosis: a Korean series of 96 P0Cy1 patients from an overall series of 1072 cases with serosal tumors (172 with positive cytology), revealed through multivariate analysis that N0–2 and surgery were positive prognostic factors compared to N3 and no surgery. In particular, gastric resection changed mean survival from 4 to 21 months in P0Cy1 cases [7]. Thus, in the subgroup of gastric cancer patients with only positive cytology without overt peritoneal nodules, radical resection of gastric tumor and node clearance is recommended. The main goal is of course staging, but also giving patients with no or limited node disease the chance of long-term survival. In this subgroup of patients, it is likely that adding intraperitoneal chemotherapy to surgery (HIPEC or EPIC) is reasonable; clinical trials are much needed on this topic.

Peritoneal carcinomatosis

The presence of macroscopic peritoneal involvement at pre-operative CT scan, staging laparoscopy or during laparotomy for planned radical resection, has always been associated with a very poor prognosis. However, an effort should be made to provide a better categorization of patients, for example, using the peritoneal carcinomatosis index (PCI). PCI is the sum of a carcinomatosis score ranging from 0 to 3 (LS0, no tumor, LS3 tumor > 5 cm or confluence) in 13 different areas of the abdomen in the presence of peritoneal nodules the index ranges from 1 to 39.

A growing literature shows that a very limited percentage of patients with peritoneal carcinomatosis may be treated with cytoreduction and intraperitoneal chemotherapy, usually through HIPEC. The extent of cytoreduction (CC=, no residual disease, or CC1, less than 2.5 mm residual disease) strictly influences the likelihood of long-term survival, thus representing the most important prognostic factor. This is a highly debated topic in the literature, with the results of ongoing prospective studies much waited. For the purpose of this article, we report the Italian Research Group for Gastric Cancer (GIRGC)'s official guidelines, stating that "HIPEC can be performed in selected patients having a limited

peritoneal carcinomatosis index (PCI < 6) and in selected patients with metachronous PC" [8].

The GYMSSA trial (although terminated earlier than initially planned), whose aim was to evaluate the impact of cytoreductive surgery plus HIPEC on outcomes of patients with peritoneal carcinomatosis of gastric origin, concluded that "Maximal cytoreductive surgery combined with HIPEC and systemic chemotherapy in selected patients with gastric carcinomatosis and limited disease burden, can achieve prolonged survival" [9]. The criteria for patient selection and the precise definition of limited disease burden are still debated.

In conclusion, surgery with radical intent should not be a priori denied to all patients with macroscopic peritoneal involvement from gastric cancer, even though this subgroup would probably have the worst prognosis among all stage IV gastric cancer cases.

Distant nodal metastases

From the 2011 Japanese Classification of Gastric Cancer, 3rd edition [10], lymph node stations 1–12 and 14v (as well as stations 19, 20, 110, and 111 for cancer of the esophagus) are defined as regional gastric lymph nodes; metastasis to any other nodes is classified as M1. Thus, pancreatic head nodes (stations 13 and 17), superior mesenteric artery nodes (station 14a), middle colic artery nodes (station 15), pancreatic tail nodes (station 18), and para-aortic nodes (station 16), when affected by the disease, represent distant metastases and are categorized as M1 (stage IV). This taxonomy is one of the most clinically relevant issues discussed between Eastern and Western surgeons. While in Eastern centers, lymph node dissection in these areas is currently under study after being nearly neglected for many years due to poor prognosis, in Western centers lymph node dissection is frequently extended, especially in high-volume gastric cancer centers, to the retropancreatic nodes and especially to the periaortic nodes.

Interestingly, in the early 70s and 80s, Japanese surgeons set the example showing how an aggressive surgical approach to gastric cancer, mainly in terms of lymph node clearance, would benefit a large proportion of patients with node spreading tumors, whereas Western surgeons accepted and learned to perform this type of surgery only a few decades later. At the same time, Eastern surgeons did recognize that in most cases of well-differentiated and low-staged cancer, extended node clearance would not be necessary. Thus, the D2 lymphadenectomy was and is limited to stations 1–7, 8a, 9, 10, 11p, 11d, and 12a for total gastrectomy and to stations 1–7, 8a, 9, 11p, and 12a for distal gastrectomy. The so-called D2+, or D3 lymphadenectomy, is not recognized in the 2010 Japanese gastric cancer treatment guidelines [11].

It is true that very far nodal metastases, such as axillary, inguinal, and clavicular nodes, have the same biological origins of hematogenous metastases, although they are not suitable for surgery without intent of exclusive palliation. However, a small number of studies in Western patients finally confirmed from the pathological point of view that extra-loco-regional nodes are frequently involved by metastatic cells as the only tumor burden. A study published by the Italian Research Group for Gastric Cancer in 2007 [12] analyzed the incidence of nodal metastases in each nodal station according to tumor location and T stage; it showed that station 16 nodes are positive in 38% of T4-upper third, and in 30% of all upper third cancers (and in 12 and 9% of middle and distal third cancers, respectively). A significant proportion of these patients has no other extranodal metastatic sites; thus, they may be suitable for R0 surgery.

Indeed, one of the few papers analyzing the risk factors for survival in patients undergoing surgery for metastatic gastric cancer—a Chinese series of 872 cases observed from 1993 to 2008 with hematogenous and distant nodal metastases—clearly showed that in the subgroup of patients with nodal-only disease (outside from loco-regional nodes), "radical" surgery was a significant prognostic factor for improved survival [13]. This may suggest a possible revision of the classification of periaortic metastases in stage IV, because also Eastern surgeons seem to agree that such patients may be surgically treated with survival benefit; this strategy is now the tentative standard, mentioned in the 4th version of the Japanese Gastric Cancer Treatment Guidelines as one of the current clinical questions [14]. In addition, a Japanese phase II trial exploring a treatment strategy with neoadjuvant chemotherapy followed by D2+ para-aortic nodes dissection for patients with metastases in para-aortic nodes showed excellent results in terms of survival [15].

Hematogenous metastases

Metastases in distant organs should be classified in liver and no-liver diseases. To the best of our knowledge, there is no evidence of pulmonary, bone, brain, etc., metastasectomy with curative intent in gastric cancer patients. There are some reports about the resection for pulmonary metastases without any significantly increasing survival rate [16, 17]. The only distant metastasis site which is accepted for surgical treatment is ovarian cancer (the so-called Krukenberg disease), whose pathogenesis is, however, somewhat different from that of pure hematogenous metastases. In contrast, hepatic metastases may represent the unique site of hematogenous spread of disease due to the venous flow from abdominal organs via the portal way. A very large number of series, which analyzed the surgical treatment of hepatic metastases from gastric cancer, has been published so far, and 3 meta-analysis are available [18–20]. Both

synchronous and metachronous diseases have been analyzed. Overall, mortality related to hepatic resection is as low as 2.6% (which is not surprising given the normal liver usually observed in those patients). Meanwhile, 3- and 5-year survival rates ranging from 21 to 38 and from 0 to 38% have been reported, respectively. A global 5-year survival rate of 11% has been estimated [19].

The main problem is that there are no clear risk factors which can exclude with high degree of likelihood the possibility of long-term survival (the only one is multiple bilobar hepatic disease, while number, diameter, timing, hepatic margin, and gastric cancer T and N are not). The Italian Research Group for Gastric Cancer (GIRGC) devoted a lot of work to this topic, analyzing both the synchronous and the metachronous settings. A retrospective multicenter analysis of 195 cases of synchronous, liver-only metastases, treated with complete primary and metastatic tumor resection (R0 group, 53 patients), only gastric tumor resection (R+ group, 93 patients), or no-resection showed the following results: in the absence of the 2 risk factors significant using multivariate analysis (T3–4 and H3), the prognosis of R0 patients was as high as 80, 50, 32, and 25% after 1, 2, 3, and 5 years (cumulative survival according to Kaplan–Meier curves) [21]. Most important, in this series, the survival was significantly affected by the possibility of undergoing a chemotherapy cycle.

Another paper from GIRCG retrospectively analyzed 73 patients with liver-only metachronous metastases, who were treated with surgical resection (11 cases), chemotherapy (17 cases), or palliative care (45 cases) [22]. With the limitations due to the retrospective design, this study found T3–4, N+, and G3 as independent prognostic factors. In the absence of any risk factor, the overall prognosis was also surprisingly positive (actuarial survival rates of 80, 60, 40, and 40% at 1, 2, 3, and 5 years, respectively). In this series, a comparison was done in the small subgroup of 29 patients having only H1 and H2 metastases, thus theoretically suitable for radical surgery, who had undergone surgery, chemotherapy, or no therapy: surgical cases had significantly better mean survival times (23, 13, and 6 months, respectively), without relationship with the above-mentioned risk factors ($p=0.03$ in both groups with 0–1 and 2–3 risk factors). Thus, it is evident that a subgroup of selected patients with both synchronous and metachronous liver-limited metastases from gastric carcinoma may be treated with potentially curative surgery delivering survival benefit.

Conclusions and discussion

Stage IV gastric cancer patients represent a subgroup of patients with poor prognosis and surgical treatment is usually limited. Indeed, there are no evidence-based indications to surgery, and oncologists are often reluctant in sending those patients for a surgical consultation. Recent preliminary results of the first randomized trial comparing gastrectomy plus chemotherapy vs chemotherapy alone for advanced gastric cancer suggest that gastrectomy cannot be justified for treatment of patients with these advanced tumors [23]. The possibility of severe post-operative morbidity and even of mortality should be taken into account when dealing with metastatic cases, because surgery has obviously the potential to be harmful. For instance, a recent small series of Western patients treated with surgery + HIPEC for P0C1y gastric cancer reported a mortality rate of 18%, operation time close to 400 min, and median length of hospital stay of 14 days [24]. This burden may be too much for patients undergoing chemotherapy as the most important weapon for prolonged survival. Other papers investigating if surgical stress associated with palliative gastric cancer resection shortens their survival concluded that in-hospital mortality was higher in non-resected patients (15.9 vs 3.4% for surgically treated patients) [25].

Meanwhile, based on the existing evidence, we cannot exclude with high degree of likelihood that a stage IV patient, who undergoes radical surgery within an integrated therapeutic path including chemotherapy, will not have the possibility of long-term survival. In a recent Korean series of 273 patients, all undergoing chemotherapy for metastatic disease, 42 were finally treated with R0 gastric and metastatic disease resection, and 12 out of 42 (4.3% of the whole series) were free of disease at a median follow-up of 29.1 months [26]. Unfortunately, there are no single risk factors, or combination of risk factors, able to identify those 12 patients, who would really benefit from extended surgery. A 2012 study designed to determine the influence of clinical–pathological and treatment factors on survival in gastric cancer patients with distant metastasis after gastrectomy, showed through multivariate analysis that the status of liver metastasis, as well as other variables including gender, age, location of tumor, Bormann type, depth of tumor invasion, lymph node involvement, peritoneal dissemination, number of metastatic sites, pathological differentiation, and types of gastrectomy, and were not independent prognostic factors for survival [27]. Indeed, some interesting results have recently been reported in metastatic patients undergoing surgery: in a retrospective chart review from a Western institution (MD Anderson Cancer Center), which investigated 7484 patients with gastric cancer between 1995 and 2012, 82 patients surgically treated were identified: their 5-year overall survival was 42% for positive cytology, 13% for carcinomatosis, 34% for distant nodes, and 20% for hepatic metastases [28].

The aforementioned Japanese retrospective study [6] concerning the long-term survival of stage IV gastric cancer patients, who underwent surgical conversion therapy (defined as "the surgical treatment aiming at an R0 resection

after chemotherapy for tumors that were originally unresectable or marginally resectable for technical or oncological reasons"), showed that the MST for the patients, who received either a treatment-oriented or a palliative surgery conversion therapy, and is higher for all the categories considered, and that the MST of R0 resected patients is higher than the MST of R1/2-resected patients.

This topic is still highly debated in the literature and more studies are needed to define how to select the patients for surgery which patients have the best chance of long-term survival [29, 30]. In conclusion, as stated in a recent work [31], it is likely that the main determinants of medium- and long-term survivals in stage IV gastric cancer would be the complete removal of tumor associated with pre-operative chemotherapy and the selection of patients who do not display tumor progression during chemotherapy.

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Compliance with ethical standards

Conflict of interest All the authors declare that there is no potential personal conflict of interest or financial disclosures.

Research involving human participants and/or animals The guidelines provided by the Committee on Publication Ethics (COPE) have been followed. This article does not contain any studies with human participants performed by any of the authors.

Informed consent All the authors declare that the material has not been previously published or submitted elsewhere for publication and will not be sent to another journal until a decision will be made concerning publication by your journal, since the manuscript is a review of the literature, no informed consent was obtained.

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