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REVIEW ARTICLE

The role of surgery in the therapeutic approach of gastric cancer liver metastases

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Abstract Gastric cancer (GC) currently prevails as the second cause of death by malignancy worldwide. Estimations suggest that 35 % of affected patients appear with synchronous distant metastases. The vast majority of patients present with hepatic metastatic disease, sometimes accompanied by synchronous peritoneal and lung dissemination. The disease mostly remains asymptomatic at an early stage, with few reported cases of incidental abdominal discomfort. As the cancer advances, symptoms such as nausea or vomiting arise, along with indigestion and dysphagia, blood loss in the form of melena or hematemesis, as well as anorexia and weight loss. Having spread to the liver, it also causes jaundice due to hepatomegaly and general inanition. Despite recent research on the therapeutic strategies against GC metastatic disease, surgical resection appears the only potentially curative approach. Unfortunately, the majority of patients are not eligible to undergo surgical intervention. With regard to treatment modalities of the advanced stage disease, the role of metastasectomy is still debatable and quite unclear, while prolonged survival was succeeded only under certain specific circumstances. Systemic chemotherapy remains however another option, as well as local management in the form of cryotherapy, radiofrequency ablation, or transcatheter arterial chemoembolization. The aims of this review were to evaluate the results of surgical treatment for metastatic GC with special reference to the extent of its histological spread and to present the recent literature in order to provide an update on the current concepts of advanced surgical management of this entity. Relevant publications in the last two decades are briefly reviewed.

Keywords Diagnostic modalities · Gastric cancer · Liver metastatic disease · Surgical strategy · Therapeutic approach

Introduction

Gastric cancer (GC) currently prevails as the second cause of death by malignancy worldwide, mainly due to its lack of early presenting symptoms and the absence of widespread screening schedules [1, 2]. In fact, estimations suggest that 35 % of affected patients appear with synchronous distant metastases [3, 4]. The vast majority of patients present with hepatic metastatic disease, sometimes accompanied by synchronous peritoneal and lung dissemination [5, 6]. Apart from the tumor necrosis factor (TNF) classification, we also refer to the hepatic (H) factor regarding liver metastasis as follows: H0=no liver metastasis, H1=limited to one lobe, H2=small number of metastases in both lobes, and H3=many metastases in both lobes. Metastatic disease to the liver may remain asymptomatic at an early stage or present with abdominal discomfort, hepatomegaly and jaundice [7, 8]. Concerning the most prevalent diagnostic modalities computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are implemented to unveil hepatic metastases [9, 10]. Despite recent research on the therapeutic strategies against GC metastatic disease, surgical resection appears the only potentially curative approach. Unfortunately, the majority of patients are not eligible to undergo surgical intervention. With regard to treatment modalities of the advanced stage disease, the role of metastasectomy is still debatable and quite unclear, while prolonged survival was

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succeeded only under certain specific circumstances [11]. The aims of this review were to evaluate the results of surgical treatment for metastatic GC and to present the recent literature in order to provide an update on the current concepts of advanced surgical management of this entity. Relevant publications the last two decades are briefly reviewed. Mesh words selected include gastric cancer, liver metastases, hepatectomy and surgical strategy.

Diagnostic modalities

Latest epidemiological data support that among GC patients who undergo initial therapy with surgical resection, an average of 25 % to 30 % will eventually be diagnosed with metachronous liver metastatic disease. As a result, it is estimated that the liver, consisting the most common metastatic site, will inevitably be affected in 50 % of the cases during the course of the nosologic entity [12]. The diagnosis of the sites of distant liver metastases and the recognition of the lesions' specific characteristics are mainly accomplished with helical CT, MRI, and PET scan using the tracer fluorodeoxyglucose (FDG) and laparoscopy. Recent investigations suggest that FDG PET remains the most sensitive non-invasive imaging modality for the detection of hepatic metastases, especially when relevant results are interpreted in conjunction with the use of CT [13]. One major drawback is the absence of detailed anatomic information in the area of significant tracer uptake. Therefore, clinical decision making requires confirmation of the elucidated intrahepatic location as well as the specific segment involved and potential relation of the lesion with the surrounding vessels. Nevertheless, the combined CT-FDG PET strategy was ultimately found to be cost effective for patients with elevated CEA levels who were candidates for hepatic resection. However, MRI imaging enhanced with superparamagnetic iron oxide (SPIO) particles has also proved to be highly efficient, representing, after helical CT, a decent alternative to the costlier and of limited availability PET approach. Moreover, standardized protocols of image acquisition and interpretation of FDG PET surveys are warranted before this promising diagnostic technique can be widely proposed [9]. Considering its high frequency and extremely low 5-year survival rate of 0 % to 10 % in multicenter reported cases, the study of the ideal treatment modalities for this entity needs to be taken under serious consideration [3].

Surgical approach of synchronous liver metastatic disease

Based on the literature of the past 5 years concerning GC patients with a solitary liver metastasis, we conclude that there is a proven long-term survival benefit after complete surgical resection of both the gastric and hepatic lesions. It should be clearly stated that the role of careful postoperative supportive treatment is crucial, especially in cases with an advanced pathological N stage [3, 14]. In fact, active multi-agent chemotherapy is widely recommended after hepatectomy, as this combined therapeutic intervention is associated with the most favorable outcomes [15]. However, there exist prognostic factors limiting the operative feasibility for these patients, with a major one being the location of the hepatic lesion close to the hilar region and main blood vessels. Moreover, the disease is considered to have spread irreversibly when gross peritoneal dissemination occurs, which is also a major restrictive factor for surgical treatment [3]. Therefore, synchronous metastasis is not a contraindication for hepatectomy in GC patients with adequate performance status as the 1-, 3-, and 5-year cumulative survival rates of the solitary liver metastasis GC patients without peritoneal spread has been reported as 79.2 %, 33.3 %, and 23.8 %, respectively [16]. Nevertheless, in the majority of the cases, hepatic recurrence is observed, with concurrent extrahepatic relapse in half of them.

Concerning multiple synchronous metastatic sites, it is proven that even numerous liver tumors and a bilateral spread within the liver could be treated by surgical therapy in strictly selected cases as long as all tumors can be removed curatively. Recent investigations support that patients receiving hepatic metastasis resections could harvest a significant survival benefit if indications can be appropriated to perform a radical surgical procedure for both the primary tumor and secondary liver foci [17]. Clinically, it is essential to identify suitable candidates for liver resection at diagnosis. Relevant articles revealed three independent prognostic factors associated with poor survival rate, namely serosal invasion of the primary tumor, the number of hepatic lesions, and the diameter exceeding 5 cm [1, 18]. Moreover, recent researches detected that lymph node metastasis revealed a non-eligible risk factor leading to unpredictable difficulties in radical operations and increasing proportion of occult micrometastases at the time of hepatectomy, implying that the most frequent pattern of recurrence is intrahepatic. Furthermore, the role of aggressive chemotherapy is dominant as well, as initially unresectable multiple liver metastases have been totally excised following local or systemic chemotherapy [19, 20]. The option of palliative gastrectomy along with partial liver resection to reduce the tumor bulk or delay complications has also been evaluated, proving to be of no benefit on overall survival [21].

Therefore, patients who are registered as good candidates for hepatectomy are those with solitary hepatic metastasis preferably graded $H < 3$ and tumor size $T <= 2$,

whereas those to be excluded from hepatic resections are patients with T > =3 and H3 staging [15]. In addition, significant difference in the size of tumor-free resection margin with regard to the limit of 10 mm in long- and short-term survivors has been demonstrated indicating a powerful determinant of poor outcome. Recurrence rate in the remnant liver is higher in patients with surgical margin less than 5 mm. Moreover, micro-metastases around the macroscopic tumor are apparent more frequently in hepatic disease from GC in comparison with colorectal cancer confirming aggressive metastatic potential. Finally, the aggregation of lymphocytes enclosing the metastatic lesion has been reported as a favorable prognostic factor preventing further tumor extension [20]. Moreover, the presence of pseudocapsule should be considered as a protective immunoinflammatory reaction against the metastatic nodule. Encouraging studies declare that a 5-year survival rate of 20 % is achieved after curative hepatectomy, making surgical removal the treatment of choice [12].

Surgical management of metachronous liver metastatic disease

In recurrent GC, hepatic metastases are described in over 90 % of the cases in the first 2 years following gastrectomy. It is noteworthy that, according to statistics, the early presentation of hepatic metastases is not considered a negative prognostic factor [22, 23]. Multi-centered surveys elucidate that the risk parameters most predictive for GC relapse are lymphatic invasion as well as the development of a lymphaticoportal venous anastomosis due to mesenteric lymphatic occlusion [3]. Clinical and pathological variables that are considered to correlate with survival are hepatic lesions of size less than 4 cm, located in only one lobe, with the liver being the exclusive site of recurrent disease after careful and thorough imaging. Contrariwise, all available data advocate that extrahepatic concurrent dissemination, diffuse metastases of distant lymph nodes, or unresectable local recurrence are major contraindications for any surgical intervention. Furthermore, prognostic factors such as serosal invasion of the primary tumor, identification of three or more hepatic tumors, and lesion size of 5 cm or greater, are widely associated with poor survival rate, not however excluding these patients from the option of surgical therapeutic approach [18, 24]. The more efficient stage of surgical patients may explain the recorded difference in survival but, remarkably, the beneficial effect of surgery proved to be evident when analyses were restricted to sub-populations presenting with favorable (H1 and H2) or minimal hepatic involvement [16].

In several studies, the number of liver metastases was a marginal prognostic factor for survival after hepatic surgery with curative intent [25]. Relevant detection of long-term survivors with more than three metastatic lesions confirms that curative hepatectomy should not be abandoned even in patients with multiple liver nodules. With regard to lobar distribution of liver metastases, patients with bilobar lesions appear with worse prognosis compared to those presenting with a unilobar solitary tumor [8]. However, a potential correlation between the number and lobar distribution of the tumors should be revaluated in larger series. In addition, pseudocapsule formation should be considered as a protective immunoinflammatory reaction against the metastatic potential of secondary liver foci [26]. On the contrary, positive resection margin has been elucidated as a powerful determinant of poor outcome [27]. The consensus seems to conclude that there is not apparent value to surgery if residual disease remains, whether it refers to resection margins or the identification of distant metastases or peritoneal spread.

Reviewing the cases when surgical management of metachronous liver metastatic disease was performed, we come to the conclusion that the best results are associated with surgery, if a complete resection of the lesions can be achieved, while also preserving adequate postoperative liver function. Regarding the operative risk, most centers report absence of surgical complications with low perioperative mortality [18]. Consequently, surgical removal should be proposed if extrahepatic noncurable tumor dissemination can be ruled out, even when facing multiple lesions spread bilaterally within the organ [12]. Moreover, adjuvant chemotherapy after gastrectomy does not negatively affect survival after hepatic relapse, implying that recurrence does not necessarily reflect more aggressive disease. A trend toward a better survival was also observed in patients with recurrence treated with chemotherapy [28, 29]. Variations in the biologic behavior of the metastatic nodule and the host reaction rather than the surgical procedure or adjuvant chemotherapy may affect the prognosis. Results are summarized in Table 1.

Multi-disciplinary therapy for GC with metastatic hepatic involvement

Non-surgical interventions including systemic chemotherapy and local management in the form of radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), cryotherapy, and hepatic arterial infusion (HAI) have been reported to produce clinical benefits for metastatic GC patients with liver involvement [2]. Among these various local ablative methods, RFA has proven to be superior in the treatment of metastatic tumors to the liver, and

Table 1 Variations in the biologic behavior of the metastatic nodule

	Publication year	No. of patients	Synchronous lesions	Metachronous lesions	% curative surgery candidates	% 5-year survival of curative surgery	% 5-year survival of conservative treatment
Wang et al. [3]	2012	30	30	0	100	16.7	–
Takemura et al. [1]	2012	64	32	32	100	37	–
Kinoshita et al. [18]	2014	256	106	150	100	31	–
Tiberio et al. [15]	2014	212	212	0	53	9.3	0–1
Qiu et al. [2]	2013	526	526	0	4.8	29.4	–
Li et al. [21]	2009	101	101	0	0	0	0
Tiberio et al. [12]	2009	73	0	73	15	20	0
Shirabe et al. [30]	2003	36	16	20	100	26	–
Wang et al. [3]	2014	315	315	0	12.4	10.3	0
Cheon et al. [41]	2008	22	18	4	100	23	–
Nomura et al. [40]	2009	17	9	8	100	30.8	
Garancini et al. [31]	2012	67	36	31	31	19	–
Thelen et al. [39]	2008	24	15	9	75	23	–
Koga et al. [32]	2007	42	20	22	100	42	–
Sakamoto et al. [24]	2007	37	10	27	86	11	–

most clinics worldwide currently opt for this method as the most efficient alternative to surgery for inoperable liver metastasis. Regarding TACE and HAI, they may possess the advantage of good local control with delivery of high drug concentrations to the lesion; however, there is no evidence supporting a better survival in GC patients [33, 34]. According to relevant data, local treatment may efficiently play a pivotal role to the improvement of survival rates, and especially for patients with low levels of Ca19-9, a solitary liver metastasis and the concurrent administration of adjuvant chemotherapy [18].

RFA is performed percutaneously, laparoscopically, and with an open approach, and can be used in combination with surgery when a tumor-free margin cannot be accomplished through the operation alone [35]. Highlighting its advantages, it is mainly preferred for being less invasive, of lower cost, and for the fact that it is accompanied by relatively low morbidity and mortality rates, with very few minor complications reported. Namely, recent studies illustrate that the median survival of patients receiving ablation was 30.7 months, with a 5-year survival rate of 16.1 % [36]. Surprisingly enough, there even exist surgical departments who would suggest the use of RFA as primary therapy when it comes to treating metachronous GC liver metastases, also taking advantage of the fact that it can be performed several times. In conclusion, with appropriate selection of patients excluding tumor size greater than 5 cm, location of the lesions close to the hepatic capsule, the gallbladder, the hilar vessel, or the caudate lobe and cases with bile duct obstruction, RFA remains a safe and feasible therapeutic option, even when multiple RFA treatments are required [37, 38].

The review of most scientific surveys leads with certitude to the principle that an aggressive multimodal treatment associating surgery and chemotherapy should be pursued whenever clinically possible, as it offers the best survival results. Also cytoreductive surgery of non-curative gastrectomy combined with intraoperative peritoneal hyperthermic chemotherapy (IPHC) could be an option for selected patients with metastatic GC and single peritoneal dissemination [21, 39]. As regards treatment with systemic chemotherapy alone, the Japan Clinical Oncology Group 24 reported a 5-year survival rate of only 1.7 % in patients with metastatic GC confined to the liver, suggesting that monotherapy of that kind is of low utility [40–42]. We hope that more aggressive chemotherapy will expand the indications for liver resection in future cases of GC with hepatic involvement, by rendering operable previously considered unresectable tumors.

Compliance with ethical standards

Conflict of interest AM, CB, SM, ISP, ND, VS, and NA declare that they have no conflict of interest.

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