Overview on Gastric Cancer

Chapter 3

Surgical Management of Liver Metastases from Gastric Cancer

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1. Introduction

Gastric cancer is the fourth most common cancer worldwide and account for 1.5% of all new diagnoses and 5.2% of all cancer deaths [1,2]. More than 139.000 new cases in Europe and more than 951.000 new cases worldwide were diagnosed in 2012. Gastric cancer is often diagnosed at an advanced stage due to the lack of symptoms at an early stage and lack of a screening schedule throughout most of the world. At the time of diagnosis 35% of patients present with evidence of distant metastases and 4-14% have metastatic disease to the liver [3,4]. Furthermore in patients who present with local disease and undergo curative resection, the development of metastases is common, with hepatic metastases the commonest site of recurrence, occurring in over one third of patients [5,6]. The aggressive nature of gastric cancer is the reason why hepatic resection in many cases is not taken into account. Although the effectiveness of liver resection for metastatic colorectal cancer has been already established [7-9], since '90 liver metastases from gastric cancer were considered a non surgical entity. Starting from 2000 reports of hepatic resection for liver metastases of gastric cancer has been published even if rare and till today its significance is still controversial [10]. In fact a number of studies reported that the effect and benefit of hepatic resection for either synchronous or metachronous gastric hepatic metastases (LMGC) on survival was dubious [11]. Furthermore the surgical indications for liver metastases of colorectal cancer have been expanded to include all technically resectable metastases numbering 4 or more [12]. On the contrary, the surgical indications for liver metastases of gastric cancer must be carefully determined because of the more severe

biologic nature of this disease [13].

Most of patients with gastric cancer with concomitant liver metastases are excluded from candidates for curative surgery accompanied with hepatic resection due to incurable simultaneous factor such as peritoneal dissemination, widespread lymph nodal metastases and direct invasion to adjacent structures [14]. In fact LMGC often represent only a part of a generalized spread of the primary tumor ("the iceberg tip"). Furthermore very few patient with LMGC are good candidates for liver surgery due to multiple, scattered, bilobar lesions [15]. Only 0.5-10% of patients with GCLM will have technically resectable disease in the absence of extrahepatic disease. Patients with isolated metastases are unusual, accounting for 0.5% of cases in the Linhares's series [16]. On the other hand metastatic liver involvement, which occurs in up to 50% of patients with gastric cancer, makes long-term survival without treatment impossible, with a median survival of 6 months. These data growth to 7-15 months with chemotherapy schedules. There are no adequate large prospective studies detailing the natural history of metastatic gastric carcinoma and long term survival. However, two small randomized trials compared best supportive care vs. combination chemotherapy and found that no patients treated with supportive care lived for >1 year [17,18]. Survival data for patients with metastatic gastric cancer (MGC) to the liver only are also limited and the prognosis for GC patients with liver metastases is poor with 6 months survival rate of 20-50%. In a study analysing 643 patients enrolled in five separate chemotherapy trials by the Japanese Clinical Oncology Group (JCOG), 5-year survival for patients with metastases confined to the liver and treated with systemic therapy alone was 1.7% [19]. Palliative chemotherapy using various regimens has been widely used as the treatment of choice, and is considered the mainstay of treatment for metastatic disease. There have been several chemotherapy regimens described in the literature for treatment of metastatic disease, but there is currently no consensus as to which regimen provided the best response. Even with systemic chemotherapy only modest improvements in overall survival have been observed, with median survival increasing from approximately 3 months to 7–15 months. Long-term survival is rarely reported [20-22]. In particular, considering the few trials evaluating systemic chemotherapy in the subset of patients with liver-only metastatic involvement, 5-years survival rates do not reach 2% [19]. More recently there has been evidence sustaining a role of biological agents for the treatment of metastatic disease [23]. Baba *et al.* [24] have shown that the outcome for patients with non curative resection for advanced gastric cancer is extremely poor, and the optimal treatment of patients with isolated metastases without peritoneal dissemination remains open to discussion because of the biological, clinical and pathological aggressiveness of gastric cancer. In contrast to the treatment of colorectal liver metastases, there is not yet a standard multidisciplinary therapeutic approach that could have an effect on 5 years survival of these patients. Various studies show that complete surgical resection is the only form of therapy that can be employed with a curative intention. Otherwise the guidelines do not recommend surgery for stage IV gastric cancer;

according to the National Comprehensive Cancer Network Guidelines [25] surgical therapy is not recommended. Liver metastases is still considered a non-curative factor in patients with gastric cancer in classification by both the Japanese Gastric Cancer Association and the American Joint Committee on Cancer Staging. It seems that the clinical community does not include surgery among the therapeutic options for these patients, with an "aprioristic passive attitude" as reported by Tiberio et al. [26]. Although until a few years ago the Japanese Gastric Cancer Treatment Guidelines recommended chemotherapy, radiation therapy or palliative surgery for the treatment of metastatic gastric cancer [27].

Liver resection is now considered a routine procedure at speciality centres around the world: improvements in the understanding of anatomy, physiology, perioperative care and surgical techniques and technologies have reduced operative mortality in most tertiary referral centres to < 2% [28]. Recently it was revised the possibility of surgically removed metastatic lesions in order to obtain radical (R0) resection [29]. The works in literature reports a survival rate at 5-year after surgical resection of hepatic metastases ranging from 0-38% [30], but the lack of clinical trials on hepatectomy for this disease makes it difficult to draw solid conclusions relating on the most important prognostic factors. In the last 17 years several authors have reported on their limited experiences of surgical complete resection of the metastatic tumors in selected patients of LMGC [31-33], considering patients with liver metastases as sole metastatic site. However, considering survival performances extrapolated from a cohort of 1452 patients submitted to hepatic resection for noncolorectal nonendocrine liver metastases, Adam *et al.* [34] observed that metastases from gastric adenocarcinoma performed in an intermediate way, ranking 10th in a list of 18 primaries. Many retrospective case-control series have been reported. Otherwise these analyses are presented from a single centre, have small number of cases and include old cases. The quality of evidence is low with no randomised controlled trials, and most studies including less the fifty patients treated over a prolonged time period. This should reflect the highly selected nature where hepatic resection may be of benefit. to identifying patients. Even with these limitations a recent review of the literature about LMGC report a median 1-3-5 years survival on 436 patients of 62%, 30% and 26.5%, and a median survival of 17 months [35]. So even if the percentage of patients who may benefit from resection is probably small, otherwise only surgery is able to obtain long term survival, with 5 years survival rate up to 30% for metachronous liver metastases and only 6% for synchronous. Considering these data recently the Guidelines Committee of the Japan Gastric Cancer Association reconsidered the treatment of potentially resectable M1 diseases, on the basis of reports that showed favourable results [29]. In the last years several literature revision and meta-analysis has been published, proving the interest on this topic. The goal of this papers was to identify prognostic factor to select patients who could be considered ideal candidate to liver resection and should be offered hepatectomy with survival benefit . In the Long review [36] with approximately 1000 of patients, the overall survival was similar to that achieved for colorectal liver metasta-

ses fifteen years ago (1-3-5 years survival respectively of 68%-31%-27%). Moreover all the review and meta-analysis concluded that hepatic resection is associated with lower mortality and longer median overall survival than palliative treatment for selected patients with GCLM. Martella et al. [37] concluded that even if the percentage of patients who may benefit from resection is probably small, the best survival rate are associated with surgical treatment which should be chosen whenever possible. On the basis of these analysis the change of mind in the approach to GCLM sponsored by Tiberio *et al.* [38] seems to be a matter of fact, and "the seeds planted by a handful of Pioneers begin to grow". Surgical management of hepatic metastases from gastric cancer is becoming one of the hot topics in oncology community. Therefore the importance of liver resection for GCLM must be thoroughly analyzed and the determination of selection criteria for hepatic resection and conditions for long-term survival after hepatectomy for LMGC should be considered as crucial. In fact identification of prognostic factors that predict outcome following surgical resection of gastric hepatic metastases should assist in identification of patients most likely to benefit from this intervention or more importantly, assist in identification of patients unlikely to benefit. We revised the literature regarding monocentric and multi-centric studies, studies focused on synchronous metastases and review or meta-analysis.

1.1. Criteria for resection

Criteria for hepatic resection offered by Okano *et al.* [39] are broadly defined: hepatic resection is indicated in patients (1) with synchronous metastases who have no peritoneal dissemination or other distant metastases and (2) with metachronous metastases, but no other recurrent lesion. Ambiru *et al.* [11] added a third criterion, (3) complete resection of hepatic metastases with acceptable postoperative hepatic function. In a recent report by Roh *et al.* [40], hepatic resection is said to be indicated only in patients with hepatic metastases in one lobe of the liver without peritoneal dissemination, hilar node metastases or distant metastases. Criteria actually accepted for resection of hepatic metastases from gastric cancer are now as follows: 1) good control of the primary tumor and complete resection of primary tumor and lymph nodes involvement in synchronous disease; 2) no signs at preoperative work up of disseminated diseases, hilar lymph nodes metastases, peritoneal dissemination or extrahepatic metastases; 3) complete resection of hepatic metastases (macroscopically no residual tumor). Following these selection criteria Ochiai *et al.* [41] found a hepatic resection incidence of 21 in 6540 patients (0.3%) with a gastric cancer who underwent a gastrectomy. Saiura *et al.* [42] found an incidence of 10 in 1807 similar patients (0.6%), and Okano *et al.* [39] found an incidence of 19 in 807 patients (2.4%). A recent literature review reported only 229 liver resection for LMGC, maybe reflecting an a priori passive attitude toward these patients. Some study report a classification of degree of liver metastases in patients with LMGC according to the Japanese Classification of Gastric Carcinoma [43]: H1: metastases were limited to one of the lobes; H2:

there were a few scattered metastases in both lobes; H3: there were numerous scattered metastases in both lobes.

Independent prognostic factors analyzed in the literature identify a miscellaneous variables that can affect prognosis: unilobar distribution, number of metastatic nodules, presence of Glisson's capsule invasion, tumor size, R0 resection, synchronous or metachronous disease, pseudo-capsule formation and stage of primary tumor. In general hepatic resection is indicated when surgical procedure is not particularly invasive, practiced with radical plans and without evidence of extrahepatic disease [39]. Unfortunately, most hepatic metastases from gastric adenocarcinoma are multiple, bilateral, and combined with peritoneal or lymph nodes metastases, which directly invade adjacent organs precluding a radical surgical approach. The resectability rate is low and about only 20 % of the patients with liver metastases can be treated surgically in a situation where only patients with potentially resectable disease are referred, a situation possibly encountered at the surgical department in high-volume cancer centre [30].

In addition to factors closely associated with the metastatic lesion, the characteristics of the primary tumor are of significant importance in the therapeutic decision. The prognostic aspect of gastric cancer with liver metastases is not well clarified. The detection of liver metastases from gastric cancer occur in approximately 3% to 14% at the diagnosis of primary tumor [44] and in up to 37% of patients following gastrectomy [45]. Some studies compared the effectiveness of the liver resection, even for synchronous lesions, to palliative treatments. Hepatic resection is associated with a significant reduction in mortality at 1 and 2 years [46-48]. Although the data come from non-randomized studies, difficult to perform because of the paucity of patients recruitable, it is undeniable that surgical resection lead to a real benefit in terms of survival compared to those patients treated with chemotherapy alone. Recent chemotherapy protocols for liver metastatic gastric cancer have not yet led to satisfactory results with a median survival of 12 months and 3-year survival rate around 5% without surgery [49].

In many cases clinicians hesitation is associated to the fear that the hepatic resection can affect quality of life, nutritional and physical condition of patient postponing adjuvant chemotherapy. Although the clinical benefit of hepatic resection for metastases from gastric cancer is not widely accepted , several studies confirmed an improvement in prognosis with surgical treatment. A systematic review [36] involving 994 patients showed a median overall survival of 21 months for surgery compared from 11.3 to 13.8 months for patients in a large randomized trial who received only combination chemotherapy [50,51]. Miki *et al*. [52] retrospectively compared, even if in a limited number of patients, three different therapeutic strategies in patients with liver metastases from gastric cancer: gastrectomy plus hepatic resection, palliative gastrectomy and chemotherapy alone and concluded that gastrectomy plus hepatectomy might be a promising treatment options with 5-year survival of 36.7% for resected patients versus 15.4% for palliative gastrectomy and 0% for chemotherapy alone. To date is ongoing in Japan

and Korea a prospective randomized trial that aims to evaluate the role of gastrectomy in the management of incurable advanced gastric cancer. Patients with advanced gastric cancer diagnosed as having a single non-curable factor are randomized to gastrectomy plus chemotherapy or chemotherapy alone. The study includes patients with hepatic metastases till four lesions with a maximum diameter of 5 centimeters [53]. The results of this trial will lead to more solid data.

Hired a possible survival benefit after surgery, carefully assessment of surgical indications it is of crucial importance to clarify the condition of 5-years survival. The actual criteria include the absence of peritoneal or other metastases on pre-operative imaging, adequate physical condition , radical resection of metastases with preserved liver function. Furthermore the presence of a single lesion, disease-free margins, low stage of primary tumor, absence of lymph node or venous invasion appear to be factors that lead to a better prognosis [48]. In addition it must also include the possible response to neo-adjuvant chemotherapy in patients who received it. A progression of disease after therapy can be considered a significant adverse prognostic factor [54].

To date the results in the literature on the treatment of liver metastases from gastric cancer appear in parallel with the results obtained for colorectal liver metastases, but should be viewed with caution [55]. The studies on the topic consist in small institutional series and with patients highly selected. A recruitment of a growing number of patients enrolled to hepatectomy, after a careful multidisciplinary assessment will clarify and confirm the therapeutic role of surgical resection for liver metastases from gastric cancer.

1.2. Assessment of survival outcomes

The effectiveness of hepatic resection has not been well defined. In addition the clinicopathologic characteristic related to the prognosis of gastric cancer with hepatic metastases have not comprehensively identified. Nevertheless the presence of hepatic metastases is a statistically significant poor prognostic factor for patients with gastric cancer [14].

The cumulative survival rate reported in early studies was generally poor, reflecting a generalized disease. Elias et al. showed that the 3-years survival after hepatic resection was less than 20% [56]. In recent series the 1-year survival rate ranged from 42% to 90% and 5-year survival rate from 0% to 38% (see **Table 1**). The long-term results after liver resection for metastases from gastric cancer show a wide range (**Table 1**). Most studies concerning this issue come from Japan and the reported long-term survival rates exceed 30% in some series [8,33,57]. In contrast, in the western study from Zacherl et al. none of the patients survived five years after resection [58]. Otherwise in recent report form western countries the 5 years survival rate was of 19 and 27% [47,59].

Thus, the clinical benefit of resection of hepatic metastases from gastric carcinoma is still not widely accepted. However, non surgical treatments, including systemic or hepatic artery infusion chemotherapy, do not achieve satisfactory results. In patients treated by gastrectomy and chemotherapy, median survival times are reported to range from 2.9 to 11.8 months [60,61].

Furthermore Bines et al. [62] reported one long-term survivor of seven (14.3%) and other series showed 11.1 to 19% long-term survivors. Although few, the long-term survivors after hepatic resection do exist. Therefore to determine the indication of liver surgery is crucial and to clarify the condition of 5-year survivors..

2. Prognostic Factors

An attempt to define criteria for selection of patients with favourable outcome has been previously made in various series. We herein report a comprehensive review of the literature experience of small and selected populations series. We classified the characteristics predictive of good or poor outcome according to the primary tumor, the metastases and the type of surgery (**Table 2**).

2.1. Predictive of outcome related to primary tumor

Ochiai *et al.* have shown how the presence of serosal invasion by gastric cancer is the only significant determinant at synchronous resection and both lymphatic and venous invasion were significant prognostic factors available after histological examination [41]. Therefore the presence of serosal invasion at the time of the primitive resection should be considered a worse prognostic factor in case of synchronous and metachronous metastases, while the presence of positive lymph nodes and microscopic venous infiltration should be taken into account in case of metachronous metastases, as confirmed by the study of Morise *et al.* [63]. Also a recent multicentric Japanese analysis of long-term outcome after surgical resection for gastric cancer liver metastases stressed that the present of serosal invasion of primary gastric cancer is a poor prognostic factor [64]. The serosal invasion of primary GC is the first step in the advancement to peritoneal dissemination and thus considered as a significant poor prognostic factor after GCLM resection. These data were confirmed in the studies of Shinohara, Kostov and Takemura [65-67]. Further more Shirabe showed that lymphatic and venous invasion of cancer cells from primary gastric cancer are clinicopathological prognostic factors of poor outcome at both univariate and multivariate analysis [68]. In a recent paper Sekiguchi et al. analyzed the risk factors associated with lymphatic and venous involvement in patients undergoing endoscopic resection for gastric cancer and concluded that the papillary histology of primary tumor may have a negative prognostic role on neoplastic venous and lymph nodes dissemination. He also reports a case of liver metastases in a patient not subjected to surgical resection [69]. This could give a further confirmation of the worse prognosis for patients

with venous or lymph node tumor invasion also in early gastric cancer, although the data are preliminary and will require confirmation. Other authors emphasized and confirmed that the presence of lymph nodal tumor invasion negatively impacts on prognosis [42,70]. Imamura *et al*. [31] reported the grade of differentiation of the primary tumor as a poor prognostic factor. Koga et al. [57], Takemura *et al.* [67] stated as a serosal invasion (T4) of the primary gastric cancer is an unfavorable prognostic factor after hepatic resection. Also Tiberio *et al.* [71] in a multicentric report supported the fact that the presence of locally advanced gastric lesion (T4) and a non-radical resection in the synchronous setting suggests prudence and probably abstention from hepatectomy. Zacherl *et al.* [58] reported that tumor localization of primary gastric cancer (proximal third versus distal two-thirds of the stomach) was a marginal predictive negative factor for overall survival, while in the study of Tsujimoto *et al.* [72] the gastric cancer size greater than 6 cm was considered a predictor of poor survival. A prospective study found that in patients who underwent hepatic resection combined with the removal of primary gastric tumor, lymph node ratio may have a prognostic role. A high limph node ratio had significantly shorter overall survival than those with low lymph node ratio [73]. Elevated lymph node ratio was significantly associated with advanced pN stage, larger primary tumor size, the presence of microvascular invasion and neoadjuvant chemotherapy [36]. Also the presence of the positive peritoneal washing liquid is considered a negative prognostic factor and several authors reported no benefit in terms of survival following surgical resection [74,75].

However, some studies showed these were not significant prognostic factors and are still controversial. Miyazaki [70] and Okano [39] reported that there was non significant difference in term of depth of invasion or lymph node metastases of the gastric cancer between surviving and non surviving patients. Koga [57] reported a marginal significance of the serosal invasion of the primary tumor. Even in more recent studies with more than 30 cases [76,77] serosal invasion was not considered as a prognostic factor. More over the multi-centric studies from Komeda [78], Markar [55] and Oki [79] not attributed to serosal invasion a prognostic significance.

2.2. Predictive of outcome related to metastases

The analysis of prognostic factors related to metastatic lesion has highlighted among the most important: number of lesions and the status of resection margin has been confirmed in a recent meta-analysis by Markar *et al.* [55].

The number of the metastatic nodules in the liver has been reported to be an important prognostic factor in 18 mono-centric and 3 multi-centric studies. Okano *et al.* [39] reported 3-year survival rates of 56% for single metastases and 0% for multiple metastases, and the number of liver metastases was a significant prognostic factor in other reports as well. In Koga *et al.* [57] and Shirabe *et al.* [68] studies none of the patients with multiple gastric liver metas-

tases (three of more lesions) survived beyond 3 years, whereas the 5 year survival rate for the patients with solitary liver metastases was 55% with eight long-term survivors. Aizawa *et al.* [80] analyzed the prognostic factors of 74 patients undergoing liver resection for synchronous metastases and detected as the presence of a single lesion is the most significant prognostic factor. In fact, dividing the patients into two subgroups "solitary or multiple metastases" the median 5-year survival is 24.2 compared to 12.6 in the second group. Okano *et al.* [39] reported for a group of patients with synchronous and metachronous disease a 3-year survival rates of 56% for single metastases and 0% for multiple metastases, as confirmed a few years later by Ueda *et al.* [81]. Shirabe *et al.* [68] described the presence of three or more tumors as an independent poor prognostic factor according to both univariate and multivariate analysis; moreover, all four patients who survived beyond 5 years in their study also had solitary tumors, and almost all patients described as long-term survivors had a solitary liver metastasis. This data were confirmed in the study of Sakamoto [33] with a survival of 56% for solitary lesions against none long term survivor in case of multiple tumors. In a more recent study Sakamoto [82] showed against the value of solitary lesion adding the unilobar distribution as good predictive factor for survival of patients, as previously reported in the Miyazaki's paper [70]. Recently Schildberg *et al.* [76] and Wang *et al.* [83] confirmed in their studies as a single metastases is a favorable prognostic factor. Schildberg [76] reported a significantly better median survival for single metastases versus multiple metastases (21 vs 4 months) in a large-scale multi-institutional retrospective cohort study with a large sample of 256 patients and Wang [83] In said that a single lesion was a independent favourable prognostic factor at multivariate analysis. Furthermore, Takemura *et al.* [67] also reported good results with a 5-year survival rate and MST of 37% and 34 months, respectively in candidates with three or fewer liver metastases. In some study the number of liver metastases was a marginal prognostic factor for survival after hepatic surgery with curative intent. The favourable survival outcome for patients with a solitary metastasis, which was no worse than that for a solitary metastasis of colorectal cancer, indicates that patients with a solitary metastasis of gastric cancer are good candidates for surgical resection . On the other hand, the surgical indications should be considered more carefully in patients with multiple metastases of gastric cancer than patients with multiple metastases of colorectal cancer.

From the literature seems to emerge the fact that in all cases a long survival patients are carriers of a single lesions. Otherwise, *Saiura et al.* [42] showed two long-term survivors longer than 5 years with more than three metastases concluding that if the curative resection (R0) can be achieved, hepatic resection should not be abandoned even in patients with multiple liver metastases. According to previous paper of Saiura [42], Dittmar *et al.* [47] concluded their study stating that multiple 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. Kinoshita *et al.* [64] reported a series in which some patients underwent surgical liver resec-

tion for three or fewer liver metastases detected at preoperative diagnosis. The results stated that no solitary metastases but 3 or more hepatic tumors was an independent prognostic factor. In the last years Shinohara [65], Tatsubayashi [84] and Ohkura [85] confirmed the role of number of lesions as a prognostic factor. Ohkura [85] reported that hepatectomy offers superior survival compared with non-surgical treatment for <3 metastatic tumors with diameters <3 cm from gastric cancer. Otherwise the indication of tumor size (<3 cm) for hepatic resection is, however, not obligatory since several studies reported favourable prognosis for the patients with tumors 4–5 cm in maximum diameter. Oki *et al.* [79] recently reported that solitary metastasis was an independent prognostic factor in a large-scale multi-institutional cohort study. Moreover in all the other multi-centric studies the number of liver lesions was a predictor of outcome.

As for the lobar distribution of liver metastases, patients with bilobar tumors had a worse outcome than patients with a unilobar tumor, as shown by Zacherl and coll. [58]. Tiberio *et al.* [48] describe as the hepatic involvement (H3) worsened the prognosis of patients in synchronous metastases setting. Also Liu *et al.* [86] confirmed that the extension of liver metastases was an independent significant prognostic factor for poor survival. However, the number and lobar distribution of the tumors were correlated, and so the significance of the lobar distribution of tumors as a prognostic factor should be re-evaluated in larger series. Furthermore the distribution of metastatic lesions in many cases is a discriminating factor in order to obtain a radical resection (R0). R0 resection is mandatory, it must be the goal that the surgeon arises to reach in the pre-operative planning of these patients. Radical resection is a major prognostic factor that impacts significantly on long-term survival.

Moreover several studies take into account the dimension of liver metastases as a possible prognostic factor. Kinoshita *et al.* [64] showed as the patients with more than 3 metastases or lesion larger than 5 cm had a worse prognosis as well as reported by Ohkura [85] for more than 3 lesion of more than 3 cm. The same data were reported in multi-centric analysis of Oki [79] and Kinoshita [64].

Concluding as regard the histologic characteristics of liver metastases from gastric cancer, lymphocytes aggregation, enclosing the metastatic tumor, is reported as a good prognostic factor by Fujii [87]. This could be explained with the favourable action of TILs (tumor infiltrating Lymphocytes) in preventing tumor extension in gastric cancer patients [88]. Okano [39] demonstrated that the presence of a fibrous pseudocapsule around liver metastases is a promising indicator of a better prognosis, being closely associated with patient survival. The paper reported an actuarial 1-year and 3-year survival rates of 87% and 51% for patients with a fibrous pseudocapsule and 57% and 0% for patients without it. Pseudocapsule formation should be considered as a protective immunoinflammatory reaction against the metastastic nodule reflecting the host defence reaction creating a wall which stop tumor diffusion as re-

ported in the paper of Garancini et collegues[59].

2.3. Predictive of outcome related to surgery

Surgical margin >/10 mm in hepatic resection was a good prognostic factor in some papers. Miyazaki [70] demonstrated significant differences in the number of hepatic metastases (solitary of multiple) and the size of the tumor-free resection margin (<10 mm or >10 mm) for long and short term survivors. Thelen [32] reported that a positive resection margin should be considered a powerful determinant of poor outcome. Nomura [89] showed that the recurrence rate in the remnant liver was higher in patients with a surgical margin less than 5 mm.

The consensus seems to be that there is not apparent value to surgery if residual disease remains, whether it is involvement of resection margins, other distant metastases or peritoneal carcinosis.

The relationship between the extent of hepatic resection and prognosis has not yet been established. Isono [90] reported that micrometastases around the macroscopic tumor were found more frequently in hepatic metastases from gastric cancer than in those from colorectal ones, thus suggesting that wider surgical resection margins are required. A positive resection margin is also not an independent prognostic factor in colorectal liver metastases because of its strong relationship with the number of tumors resected. In approximately 70% of patients, recurrent disease developed after hepatic resection, most commonly in the liver. Recurrent tumors were more frequently distributed in both lobes than in the resected lobe, suggesting that liver recurrence is more probably derived from multiple metastatic foci from the primary disease than from intrahepatic tumor regrowth. As regard Nomura [89] underlined the role of intrahepatic micrometastases around liver as a cause of recurrence of the disease, pointing out that about 50% of patients with metastatic gastric cancer at the time of liver resection has already micrometastases. They stated that the presence of micrometastases was associated with poor results in term of survival after liver resection. This confirms how hepatic recurrence is associated with systemic spread through vessel or lymphatic circulation of the primary tumors. A generous surgical margin may not be essential for curative hepatic resection of liver metastases, even if in the study of Ambiru [11] a margin less of 10 mm is considered a poor prognostic factor for survival. Nevertheless a positive surgical margins should be avoided and the surgeon should strive to obtain an adequate margin, because this is the only prognostic factor on which the surgeon could have any influence over. According to the pattern of recurrence, relapse developed most commonly in the liver (70% range 63.6%-83.3%), indicating that the remaining liver should be a focus for relapse monitoring. The importance of the size of surgical-free margin was highlighted by other authors, whom showed how also a lower margin to < 5 mm can be regarded as negative factor both in terms of recurrence that of long-term survival [32,59,89]. Hired the need to maintain an adequate surgical-free margin from meta-

static lesion, emerged from the literature such as the size of the single metastatic lesion are not negligible in prognostic term. Kinoshita et al.[64] on a total of 256 patients enrolled in the multi-centre analysis identified the size ≥ 5 cm as an independent predictor of poor prognosis in term of overall survival.

The size of ≥ 5 cm as a poor prognostic factor was previously reported by Fujii *et al.* [87] and reconfirmed in some recent studies [67,78], but the data has not been confirmed by other authors [67,70,82,86].

In the more recent paper surgical margin has not been taken into account as a potential prognostic factor. Only the multi-centric study from Tiberio *et al.* [48] showed that R0 resection of the tumor bulk was a major prognostic factor and suggested that no effort must be spared to achieve it.

2.4. Timing of hepatic resection

The detection of a synchronous or metachronous metastases can be considered as a discriminating to perform surgery? At present we think was no. Until a few decades ago some paper reported synchronous disease as a significant poor prognostic factors. In fact they showed a significantly longer survival in patients with metachronous metastases than in those with synchronous disease. Ambiru *et al.* [11] reported a 3-year survival of 29% for metachronous versus 6% in synchronous lesions. Bines *et al.* [62] suggested a median survival of 8 months for synchronous disease and emphasized such as metachronous resection of isolated disease and multiple resections of recurrent isolated disease may have value in carefully selected patients. So some author suggest that resective treatment may be indicated only for the patient with metachronous isolated metastases [41,70]. A 3-year overall survival rate of 60% for metachronous versus 18% for synchronous disease was documented by Okano *et al.* [39], they also affirmed that a surgical approach for multiple and synchronous metastases may be of value as a part of combination therapy in carefully selected patients. Recently Schilberg et al. [76] against the trend of recent literature on the topic suggested a significant benefit for patient group with metachronous and solitary liver metastases, provided that R0 resection has been achieved. They reported a 5-year survival rate of 29% for metachronous versus 0% for synchronous metastases. In the last decade, many of the published studies seem to lead a changing in the surgical attitude for patients with synchronous metastases from gastric cancer (**Table 3 and 4**). Although most of the case studies were small series of patients and well selected and reported survival for synchronous lesions suggests that the en-bloc resection of the primary tumor with metastatic liver lesions leading to an improvement in survival. An analysis of the data reported in the recent literature showed that more than half 5-year survivors underwent a synchronous hepatectomy. In fact the recent meta-analysis of Markar *et al.* [55] that included 227 patients, 112 with metachronous and 115 with synchronous hepatic metastases demon-

strated no significant differences in 5-year overall survival for both groups. Other studies did not demonstrate any differences in term of survival among the groups; Cheon *et al.* [60] and Tsujimoto *et al.* [72] didn't observe a significant difference in survival between synchronous and metachronous metastases. Baek *et al.* [91] showed a 3-year overall survival for synchronous of 33% versus 38% for metachronous liver disease and they didn't find any significant factors that affected survival, probably for the limited number of patients examined. Recently the analysis of Qiu *et al.* [92] on 25 patients underwent synchronous hepatic resection reported a fifth of those alive at 5 years with an 1-,3- and 5-year overall survival of 96.0%, 70.4% and 29.4%, and recurrence–free survival rates of 56.0%, 22.3% and 11.1%. These data appear to suggest that survival for synchronous lesions, today, is not very different from that for metachronous metastases. In fact an analysis of the data reported in the recent literature showed that 27 of 55 5-year survivors underwent a synchronous hepatectomy. Also Takemura et al. [67] didn't highlights on a uniform group of patients for number (32 synchronous and 32 metachronous) any statistically significative difference in term of survival with a median of 34 months. Moreover in the Sakamoto's study [82] 3 of 5 patients who survived more than 3 years had synchronous solitary metastases and Ochiai [41] too reported three 5 years survivors with synchronous disease. In fact the studies of Qiu [92], Wang [83] and Tiberio [48] focused on the particular subset of patients with synchronous liver metastases and showed an overall survival similar to those regarding metachronous patients, offering the possibility of long-term survival. Thus, synchronous hepatectomy should not be a contraindication for hepatic resection. However it is clear that the concomitant resection of primary tumor with synchronous hepatectomy may lead to more high rate of post-operative morbidity. As regard Bines *et al.* [62] observed that synchronous resection carries a higher risk, but with no or small mortality occurred with 30 days after surgery as showed by other authors [55,92]. This may depend the concern regarding the use of aggressive liver surgery in conjunction with the treatment of gastric cancer under synchronous conditions.

Lymph node ratio may also a risk factor of prognoses among patients with synchronous GCLM who received combined surgical resection. A retrospective study found that patients with higher lymph node ratio had significantly shorter overall survival and recurrence-free survival than those with lower lymph node ratio [73]. In the multivariate analyses, higher lymph node ratio and multiple liver metastatic tumors were identified as the independent prognostic factors for both overall survival and recurrence-free survival. Elevated lymph node ratio was significantly associated with advanced pN stage, larger primary tumor size, the presence of microvascular invasion, and neoadjuvant chemotherapy. Therefore, lymph node ratio may be prognostic indicator for patients with gastric cancer liver metastasis treated by synchronous surgical resection.

However, data concerning long-term survivors demonstrate that, if we exclude bilobar

spread of metastases (H3), none of the reported predictive factors alone or in combination can deprive a patient of the possibility of long-term survival after hepatic resection, raising concern about the clinical value of prognostic factors emerging from small and superselected populations submitted to liver resection. Some data show that factors influencing survival were the extend of hepatic involvement and macroscopic peritoneal dissemination detected at surgical exploration [93,94]. When focusing on the subgroup of patients with unilobar or non disseminated bilobar metastases with negative peritoneal involvement ; the number of lesion, size of hepatic metastases and TNM stage of primary tumor were predictors of survival. All above mentioned studies strongly suggest that the main factor influencing long-term survival is the therapeutic approach to liver metastases, in particular when a surgical approach is performed. In some paper the presence of multiple poor prognostic factor displayed a cumulative effect. In the synchronous setting [48] gastric cancer T>2 and scattered bilobar metastases (H3) are negative prognostic factors: median and 5-year survival was respectively 23 months and 27% for the 10% of cases which did not display the two risk factors, while patients affected by T≥3 gastric cancer and H3 metastases (30% of cases) displayed a median survival of 6 months and did not survive more than 16 months. Accordingly, in the metachronous setting [94] the variable T4, N+ and G3 showed a negative prognostic role. Patients not presenting these variables (7%) had a 5-year survival rate of 40%, those affected by two or three negative prognostic factors (48%) had a median survival of 4±3 months.

2.5. Multi-centric studies

Based on the wind of change due to the results reported in such small single series published in literature, in the last years several multi-centric studies appeared (**Table 5 and 6**). One multi-centre retrospective analysis of 256 patients reported a promising median OS of 31.1 months [64]. Multivariable analysis identified serosal invasion of the primary gastric cancer, at least three liver metastases and liver tumour diameter of 5 cm or more as independent predictors of poor prognosis in terms of overall survival. These data has been confirmed in an Italian multi-centric study from Italian Research Group on Gastric Cancer [71]. Based on 105 patients a median overall survival of 14.6 has been reached, with an impact on survival related to T parameter and R0 resection: the Authors assumed that patients can obtain good survival performances even in presence of multiple scattered metastases in both lobes of the liver (H3), if all of them can be removed safely, pushes the tight limits in which the surgical indication is restricted in this particular field. This concept “enforces the idea that hepatic metastases may still be included in the concept of regional disease, which may benefit from regional surgery”. A propensity- matched analysis using a national database in the United Kingdom showed that the prognosis of patients who underwent both gastrectomy and hepatectomy was better than of those who received no surgery. A Japanese multi-institutional analysis from Komeda *et al.* [78] showed a median overall survival of 22.3 months and that size > 5 cm was a negative prog-

nostic factor for survival. Oki *et al.* [79] also from Japan reported a 3.3 years median overall survival in multi-centric group of 69 GCLM resected. Single tumors of less than 3 cm were the better candidates for surgical resection with a good outcome.

2.6. Review and meta-analysis

In the last years review articles follow each other with increasing frequency and almost parallel the number of research article but, fortunately, we also observe that the number of cases begins to rise. In fact, in 2010 Kerkar and *colleagues* [35] reviewed 436 patients collected from 19 surgical series published over a 20-year time-span, in 2014 Grimes *et al.* [95] reported on 438 cases and 17 papers; Romano *et colleagues* [96] on 434 and Fitzgerald *and colleagues* [97] collected 481 cases published in the period 1990 to 2013, but the last review and meta-analysis, published on line in the spring of 2016 [55], considered 991 patients who underwent liver resection for hepatic metastases from gastric cancer, recruited from 1990 to 2015. All the review concluded that in appropriately selected patients liver resection may offer a survival benefit. Where hepatectomy was undertaken, there was a significant morbidity rate but low mortality rate. The group of patients who may benefit most from hepatectomy are those with successfully treated primary disease and limited intrahepatic metastases. Those patients whose metastatic disease was synchronous, multiple or bilobar benefited less from hepatectomy, but otherwise should not be excluded from a potential treatment and than discussed on case by case analysis. In the last three years a number of meta-analysis has been published. Martella *et al*. [37] concluded that a statistically significant higher survival rate was found in the group of patients treated with local hepatic treatment of gastric cancer metastases compared to patients who underwent only palliation or systemic treatments and that curative surgery with complete resection of gastric cancer and hepatic metastases had a higher survival rate in comparison to palliative surgery of hepatic metastases or palliation. In 2016 a systematic review by Markar *et al.* [55] included 39 studies and 991 patients and concluded that is associated with 1-year, 3-year, and 5-year survivals of 68%, 31%, and 27%, respectively, and a median survival of 21 months and surgical resection was associated with better survival than other palliative treatments. Moreover number of metastases (solitary versus multiple), but not time of metastases (metachronous versus synchronous) was associated with an improved 5 years survival. Moreover Long *et colleagues* [36] concluded that compared with palliative treatment, resection was associated with significantly lower mortality at 1 year and 2 years and indicated that Asian cohorts showed higher median rates of overall survival at 1 year (73% vs 59%), 3 years (34% vs 25%), and 5 years (27% vs 17%). Moreover indicated good median overall survival rates of 68% at 1 year, 31% at 3 years, and 27% at 5 years. Median overall survival time was 21 months, which compares favorably with the 11.3 months reported for patients in a large randomized controlled trial who received combination chemotherapy of epirubicin, oxaliplatin, and capecitabine [20]. It also compares favorably with the 13.8 months reported for patients

who received both trastuzumab and chemotherapy involving the combination of cisplatin with capecitabine or fluorouracil. The last review published by Liao [98] in February 2017 suggested that hepatectomy is associated with substantially longer median overall survival than chemotherapy.

3. Repeat Resection for Recurring Metastases

The liver is the most common site for recurrence of metastases after resection for gastric cancer, with the recurrence rate of 57-87 %. It is rare that it is the sole site of recurrence and most patients receive non-curable palliative treatment. As in patients with colorectal liver metastases, a repeat hepatectomy may be considered in the absence of extrahepatic disease and if the patient has a good performance status and adequate hepatic reserve; however, repeat resection for GLM has rarely been reported. Recently, Takemura *et al.* [99] reported the result of an aggressive surgical approach for GLM including 14 repeat liver resections after 64 primary liver resections. In the report, the 5-year survival rate after repeat liver resections was 47 % which was comparable with those after the primary hepatectomy [67]. The mortality and morbidity rate were 0 and 29 %, respectively; however, the presence of severe adhesion around the liver hilum and the liver due to the previous primary lesion and liver resection concomitant with lymph node dissection makes repeat liver resection more challenging. The study demonstrated that a disease-free interval of >12 months after the initial hepatectomy predicts good patient survival after repeat liver resection. Otherwise the lack of data induce to be cautious regarding multiple repeated hepatectomy in this setting of patients

4. Conclusions

Till last years someone hold the view that liver metastatic gastric cancer represent a systemic disease and the “iceberg’s TIP” of a diffuse cancer, and surgery has no role in its treatment, because the results of liver resection are still disappointing. Worldwide the Societies for cancer treatment do not considered as a treatment for GCLM and excluded these patients from a surgical approach, with a passive attitude behaviour. Otherwise, with an analysis of series reported, mono-centric as well as multi-centric, we have found that more than 10% of patients survive more than 5 years after hepatectomy are tumor-free more than five years after liver resection, and the identification of favourable indicators of outcome could improve these results. The key of the success is to clearly identify the patients which could benefit of this treatment, in order to offer a chance of cure to the patients who have good prognostic factors and to avoid an over-treatment in case of absence of these factors. Moreover analysis of long term survival reported in literature shows that, if we exclude cases presenting a bilobar spread of metastases, none of the reported predictive factors, alone or in combination, can deprive a patient of the possibility of a long-term survival after hepatic resection. To date the results in the literature on the treatment of liver metastases from gastric cancer appear in parallel with

the results obtained for colorectal liver metastases, and the results in term of overall survival seems to be like the results obtained for colorectal liver metastases 15 years ago. So we have to expect that, as well as for colorectal metastases, with improvement of chemotherapy for gastric cancer associated with a multidisciplinary approach to these patients, an ulterior better prognosis could be achieved. The studies on the topic consist in small institutional series and with patients highly selected. A recruitment of a growing number of patients enrolled to hepatectomy, after a careful multidisciplinary assessment will clarify and confirm the therapeutic role of surgical resection for liver metastases from gastric cancer. In fact the promising results have been confirmed in a multi-centric setting with larger series. All the review articles and meta-analysis published in recent years, confirmed the superior value of surgery against palliative treatment. We believe that growing aggressive surgical treatment could provide a benefit and should be a part of multidisciplinary approach in patients with liver metastases from gastric cancer. A strong evidence that a "nihilistic" approach is no more justified for patients with GCLM emerged in the last few years. More centres shift their attitude from a passive approach to a more aggressive one, with a clear intention to treat and surgery, at least in referring centres, begins to be considered as one of the possible therapeutic options for these patients and has a role in the management of a well defined subset of metastases from gastric cancer. In fact In Gastric Cancer Treatment Japanese Guidelines nowadays has been reached the conclusion that hepatectomy could be considered in carefully selected cases of gastric cancer liver metastasis. In a recent of The EORTC and JCOG emerged that the strategy of preoperative chemotherapy followed by surgery should be further explored for resectable LMGC. Regarding unresectable LMGC, most of the sites perform chemotherapy only. However, with the future introduction of more effective chemotherapy, conversion strategies might occur. Thus, prospective data should be collected to build a basis for developing more effective treatment strategies for this population.

Compared to supportive treatment alone with a median survival of three to five months, the survival figures reported in literature indicate that liver resection can improve the prognosis of patients suffering from metastatic gastric cancer. This is true not only in Eastern experience, but also in Western countries, and in centres with skills and experience in liver surgery. A pragmatic multi-disciplinary approach, integrating neo-adjuvant and/or adjuvant chemotherapy, offers the possibility for further improvements in results.

5. Tables

Table 1: Literature analysis regarding hepatectomy for liver metastases from gastric cancer

Author year	N	Period	Resection Criteria	Resect-ability rate %	S/M	TG/ STG	Major/ Minor Liver surgery	Solitary	Multiple Uni/ BIlob	R1 %	Overall Survival % 1 3 5 ys	Long Term Survivor	Recurr-ence	morbidity/ mortality	Follow Up months
Ochiai 1994	21		No extrahepatic No carcinosis R0	Na	13/8	Na		14	7	0	19	19% (4)		na/0	na
Miyazaki 1997	21	1980-1995	No extrahepatic No carcinosis R0	na	11/10	na	5/16	7	14 11/3	Na	42 21 21	24% (5)	76.1%	na	na
Imamura 2001	17	1990-1997	No extrahepatic No carcinosis R0	na	7/10	na	6/11	8	9 4/5	18%	47 22 0	0	76%	na	Na
Ambiru 2001	40	1975-1999	No extrahepatic No carcinosis R0	na	18/22	19/21	21/19	19	21 5/16	0	70 28 18	15% (6)	75%	na/0	88
Fujii 2001	10	1979-1999	na	na	3/7	3/7	6/4	6	4 2/2	na	60 20 20	10% (1)	80%	na/0	10-240
Zacherl 2002	15	1980-1999	No extrahepatic No carcinosis R0	Na	10/5	9/6	3/12	8	7 2/5	33	35.7 14.3 0	0	90%	46%/6.7%	na
Saiura 2002	10	1981-1998	No extrahepatic ≤ 3 segments	15.6%	7/3	Na	6/4	5	5 4/1	40%	65 38 20	20% (2)	80%	na/30%	1-68
Okano 2002	19	1986-1999	No extrahepatic No carcinosis R0	17%	13/6	na	7/12	10	9 2/7	0	77 34 34	14% (3)	74%	na/0	13-148
Sakamoto 2003	22	1985-2001	No extrahepatic No carcinosis R0	8%	12/10	10/12	3/19	16	6 1/5	0	73 38 38	20% (5)	68%	na/5%	Na
Shirabe 2003	36	1979-2001	na	na	16/20	17/19	10/16	na	na	0	64 43 26	11% (4)	83.3%	na/0	NA
Roh 2005	11	1988-1996	No extrahepatic No carcinosis Solitary nodules R0	na	8/3	Na	2/9	11	0	0	73 42 27	18% (2)	80	na/0	Na
Koga 2007	42	1985-2005	No extrahepatic No carcinosis R0	17%	20/22	na	7/35	29	13	0	76 48 42	20% (8)	67%	na/5%	1-86
Sakamoto 2007	37	1990-2005	No extrahepatic R0 No carcinosis	12%	16/21	10/27	5/32	21	16 9/7	14%	60 27 11	6% (2)	81%	6%/0	Na
Thelen 2008	24	1988-2002	No carcinosis R0	na	15/9	na	8/16	13	11 5/6	25%	38 16 10	8% (2)	65%	17%/4%	1-67
Morise 2008	18	1989-2004	No extrahepatic R0 hepatic function	na	11/7	8/10	4/14	14	14	na	56.3 36.5 27	17% (3)	Na	na/0	2-200
Cheon 2008	22	1995-2005	No extrahepatic No carcinosis R0 hepatic function	7.5%	18/4	7/15	3/19	18	4 3/1	na	77 30.4 23	15% (3)	63.6%	na	1-106

Nomura 2009	17	1991-2005	No extrahepatic No carcinosis ≤ 5 lesions R0	na	9/8	Na	3/14	Na	Na	0	30.8	25% (4)	70.5%	na	1-117
Tiberio 2009	73	1990-2004	R0 no extrahepatic meta-chronous	15.1%	0/11	na	1/10	8	3	0	81 30 20	18.2% (2)	63%		4-86
Ueda 2009	72	1991-2005	na	16.6%	12/0	Na	4/8	9	3	1	57 43 43	20% (3)	na	na/0	na
Makino 2010	63	1997-2008	R0 no extrahepatic	21,00%	na	na	na	na	na	0	82 46 37	na	na	na	na
Choi 2010	14	1986-2007	No extrahepatic No carcinosis R0	Na	0/14	na	4/10	9	5 2/3	0	67 38..3	8% (1)	63%	na	na
Tsujmoto 2010	17	1980-2007	No extrahepatic No carcinosis Unilobar R0	na	9/8	Na	6/11	13	4	Na	31	30% (5)	70%	na/0	9-130
Dittmar 2011	15	1995-2009	R0 No extrahepatic	16,00%	9 6	na	2/8 5 RF	8	7 4/3		82 51 27	6% (1)	na	13%/0	01/01/59
Garancini 2012	21	1998-2007	No extrahepatic No carcinosis R0	31%	12/9	10/11	4/17	12	9 4/5	10%	68 31 19	14.2%(3)	66%	19%/0	6-90
Takemura 2012	64	1993-2011	R0 <3 mets	na	34/30	25/39	14/50	37	27	14%	84 50 37		67%	26%//0	3-174
Schildberg 2012	31	1972-2008	No extrahepatic unilobar	na	17/14	18/13	01/10/21	26	5	26%	6019 13	na	na	23%/6%	na
Yang 2012	13	2005-2008	No extrahepatic R0	na	13/0	8/05/12	06/07/12	6	7 1/6	38%	38 30 15	15%/(2)	85,00%	15%/0	2-39
Miki 2012	25	1995-2009	R0 No extrahepatic	Na	16/9	Na	Na	18	7	Na	73 43 36	Na	Na	Na	na
Aoyagu 2013	17	1995-2010	Na	22%	12/5	na	9/7	11	6 5/10	60%	75 35 17	17%(3)	Na	Na	na
Kostov 2013	28	1992-2006	R0 No extrahepatic	20%	24/4	Na	11/17	19	9 4/5	11%	68 38 28	18%(5)	83%	0/22%	12-122
Baek 2013	12	2003-2010	Solitary No extrahepatic	19%	9/3	Na	Na	11	1	8%	65 39 39	17%(2)	Na	0/0	1-85
Shinohara 2015	22	1995-2010	R0	46%	13/9	9/13	6/16	11	11 6/5	14%	82 33 26	14%(3)	Na	18%70	na
Ohkura 2015	13	1995-2014	Na	12%	9/4	Na	6/7	10	3	Na	88 30 30	30%(4)	69%	Na	1-69
Guner 2016	68	1998-2013	R0 No extrahepatic < 4 mets	Na	26/42	42/26	21/47	45	23 15/8	Na	79 41 30	Na	60%	28%/1.5%	4-189
Tatsubayas 2016	28	2004-2014	R0 No extrahepatic	Na	15713	Na	20/8	20	8	Na	91 56 32	Na	61%	0	26

S= Synchronous; M=Metachronous; TG= total gastrectomy; STG= subtotal gastrectomy;

Na: not available; mets = metastases

- number of patients resected on a total of patients with LMGC
- H3= Japanese Classification of gatric carcinoma: H1= metastases limited to one lobe; H2= few scattered metastases in both liver lobes; H3= numerous scattered metastases in both lobes

Table 2: Analysis of prognostic factors associated with survival in patients resected for LMGC

Author year	Num	age	Period	T	N	G	H	DIAM Metastases	TIMING S vs M	MARGIN	MST	Long Term Survivors	Recurrence	Recurrence free survival 1 3 5 yr	Pre-post CT	Follow Up months
Ochiai 1994	21			+	+	-	-	na	na	na	18	19% (4)	na	na	na	na
Miyazaki 1997	21	61(43-78)	1980-1995	-	-	-	+	na	-	na	11	24% (5)	76.1%	na	na	na
Imamura 2001	17	63(35-82)	1990-1997	-	+	+	-	na	+	+	16	0	76%	na	na	22.07.00
Ambiru 2001	40	63(37-75)	1975-1999	-	-	-	-	-	+	-	12	15% (6)	75%		na	88(4-296)
Fujii 2001	10	58(40-81)	1979-1999	-	-	-	-	+	+	na	16	10% (1)	80%	na	na	10-240
Zacherl 2002	15	62(37-81)	1980-1999	-	-	-	+	-	+	-	8.8	0	90%		na	na
Saiura 2002	10	55(41-70	1981-1998	-	-	-	-	-	-	na	25	20% (2)	80%	20	60,00%	29(1-68)
Okano 2002	19	69(52-79)	1986-1999	-	-	+	+	-	+	na	21	14% (3)	74%		55,00%	36(13-148)
Sakamoto 2003	22	63(52-89)	1985-2001	+	-	-	+	+	-	na	24	20% (5)	68%	na	60,00%	Na
Shirabe 2003	36	66(52-79)	1979-2001	-	Ly	-	+	-	-	-	NA	11% (4)	83.3%	na	na	NA
Roh 2005	11	52(43-79)	1988-1996	na	-	-	na	-	-	-	19	18% (2)	91,00%	na	na	Na
Koga 2007	42	64(44-89)	1985-2005	+	-	-	+	-	-	-	34	20% (8)	67%	na	33,00%	16(1-86)
Sakamoto 2007	37	64(39-76)	1990-2005	+	-	-	+	+	-	-	31	6% (2)	81%	na	18,00%	Na
Thelen 2008	24	64(41-84)	1988-2002	-	-	-	-	-	-	+	19	8% (2)	65%	33 10 10		9(1-67)
Morise 2008	18	64(51-76)	1989-2004	+	-	-	-	-	-	-	13	17% (3)	Na	na	na	117(2-200)
Cheon 2008	22	60(36-74)	1995-2005									15% (3)	63.6%	60 25 15	87,00%	15.5(1-106)
Nomura 2009	17	66(40-79)	1991-2005	-	-	-	-	-	-	+	18	25% (4)	70.5%	na	76,00%	20(1-117)
Tiberio 2009	73 (11)*		1990-2004	+	-	+	+		-	-	na	18.2%(2)	86,00%	na		15 (4-86)
Ueda 2009	72 (12)	67(25-85)	1991-2005	-	-	-	+	-	-	+	18	20%(3)	na	na	61,00%	na
Choi 2010	14	64(47-81)	1986-2007	-	-	-	-	-	-	-	NA	8% (1)	63%	na	na	na
Makino 2010	63 (13)	62(45-78	1997-2008	-	-	-	+	-	-	-	31	na	63,00%	na		na
Tsujmoto 2010	17	66.3	1980-2007	+	Ly	na	-	-	-	na	34	30% (5)	70%	na	na	29(9-130)
Dittmar 2011	15	57(25-82)	1995-2009	-	-	-	-	-	-	-	48	6% (1)	na	na	na	11(1-159)
Garancini 2012	21	64(44-89)	1998-2007									14.2%(3)	66%			6-90
Takemura 2012	64	65(32-89)	1993-2011	+	-	-	-	+	-	-	34	na	67%	42 27 27	69,00%	27 (3-174)
Schildberg 2012	31	65(35-84)	1972-2008	-	-	-	+	-	+	+	21	na	na	na	35,00%	na
Yang 2012	13	58(48-76)	2005-2008	-	-	-	+	-	na	-	12	15%(2)			85,00%	15(2-39)
Miki 2012	25	72(47-80)	1995-2009	+	-	-	+	-	-	Na	33	Na	Na	Na	35,00%	na
Aoyagu 2013	17	64(43-79)	1995-2010	-	+	-	+	-	-	na	Na	17%(3)	Na	Na	Na	na
Kostov 2013	28	68(51-81)	1992-2006	+	+	-	+	-	-	Na	Na	18%(5)	na	53 25 18	Na	48(12-122)
Baek 2013	12	61(51-74)	2003-2010	-	-	-	-	-	-	Na	31	17%(2)	Na	Na	40,00%	12(1-85)
Shinohara 2015	22	66(29-81)	1995-2010	+	-	+	+	-	-	Na	22	14%(3)	Na	42 26 26	72,00%	na
Ohkura 2015	13	64(47-71)	1995-2014	-	-	-	+	+	-	Na	Na	30%(4)	69,00%	Na	90,00%	22(1-69)
Guner 2016	68	61(30-75)	1998-2013	-	-	-	-	+	-	Na	24	0	60,00%	49 30 26	97,00%	24(4-189)
Tatsubayas 2016	28	72(39-86)	2004-2014	-	-	-	+	-	+	Na	49	7%(2)	61,00%	61 29 29	42,00%	26

S= Synchronous; M=Metachronous; TG= total gastrectomy; STG= subtotal gastrectomy;

Na: not available; mets = metastases

- number of patients resected on a total of patients with LMGC
- H3= Japanese Classification of gatric carcinoma: H1= metastases limited to one lobe; H2= few scattered metastases in both liver lobes; H3= numerous scattered metastases in both lobes

Table 3: Literature analysis regarding hepatectomy for liver metastases from gastric cancer in sinchronous setting

Author year	N	Period	Resection Criteria	Resectability rate %	TG/STG	Major/Minor Liver surgery	Solitary	Multiple Uni/BIlob	R1 %	Overall Survival % 1 3 5 ys	Long Term Survivor	Recurrence	morbidity/ mortality	Follow Up month
Wang 2012	30	2003-2008	Na	10	9/21	7/23	22	8	Na	43 17 17	16% (5)	na	12%/0	na
Qyu 2013	25	1998-2009	No extrahepatic R0	na	na	naW	16	9	Na	96 70 29	20% (5)	36%	/0	38(5-126)
Wang 2014	39	1996-2008	No extrahepatic R0	9%	5/34	Na	Na	Na 4/5	na	56 18 10	13%(4)	87%	7.7%/0	14
Tiberio 2015	52	1997-2011		na	18/35	0/52	na	na	0	60 17 11	12% (6)	92%	17/4	na
Zhoui 2016	21	1999-2010	No extrahepatic R0	2.7%	3/18	4/17	14	7	na	71 22 15	9% (2)	90%	48/0	15(3-114)

Table 4: Analysis of prognostic factors associated with survival in patients resected for LMGC in sinchronous setting

Author year	N	Period	Age	T	N	G	H	DIAM Metastases	TIMING S vs M	MARGIN	MST	Long Term Survivors	Recurrence	Recurrence free survival 1 3 5 yr	Pre-post CT	Follow Up months
Wang 2012	30	2003-2008	60(33-72)	-	-	-	+	na	Na	na	11	16% (5)	na	Na	30(100%)	
Qyu 2013	25	Na	1998-2009	-	-	-	+	+	-	na	38	20% (5)	36%(9)	56 22 11	14(56%)	38(5-126)
Wang 2014	39	64(38-81)	1996-2008	-	+	-	+	na	na	na	14	13%(4)	na	30 10 7	39(100%)	14
Tiberio 2015	52	68(	1997-2011	+	-	-	+	na	na	na	13	12% (6)	92%(49)	na	na	na
Zhou 2016	21	56(40-77)	1999-2010	-	+	-	+	na	na	na	na	9% (2)	90%(19)	na	21(100%)	15(3-114)

Table 5: Literature analysis regarding hepatectomy for liver metastases from gastric cancer: multicentric studies

Author year	N	Period	Resection Criteria	Resectability rate %	S/M	TG/ STG	Major/Minor Liver surgery	Solitary	Multiple Uni/BIlob	R1 %	Overall Survival % 1 3 5 ys	Long Term Survivor	Recurrence	morbidity/ mortality	Follow Up months
Komera 2014	24	2000-2012	No extrahepatic R0	Na	1/23	9/15	14/10	17	7	Na	78 40 40	17% (4)	66.7%	0	na
Kinoshita 2015	256	1990-2010	No extrahepatic R0	Na	106/150	99/157	73/183	168	84	10.2%	77 42 31	Na	75%(192)	10.9%/1.6%	65(1-261)
Markar 2016	78	1997-2012	Na	23%	71/7	Na	12/66	Na	Na	Na	60 42 36	Na	Na	10/	12
Oki 2016	69	2000-2010	Na	Na	28/41	Na	Na	28	41	10%	86 51 42	Na	Na	20/	25(1-142)
Tiberio 2016	105	1998-2013	Na	Na	74/31	Na	11/94	Na	Na	15%	58 20 13	12.4%(13)	82%	13%/1%	na

Table 6: Analysis of prognostic factors associated with survival in patients resected for LMGC in multicentric studies

Author year	N	Period	Age	T	N	G	H	DIAM Metastases	TIMING S vs M	MARGIN	MST	Long Term Survivors	Recurrence	Recurrence free survival 1 3 5 yr	Pre-post CT	Follow Up months
Komera 2014	24	2000-2012	Na	-	-	-	-	+	Na	Na	22.03.00	17%(4)	66.7%	Na	90,00%	na
Kinoshita 2015	256	1990-2010	Na	+	+	-	+	+	-	-	31.01.00	Na	75%(192)	44 32 30	17.6%	65(1-261)
Markar 2016	78	1997-2012	65	-	-	-	+	+	-	-	Na	Na	Na	Na	na	12
Oki 2016	69	2000-2010	Na	-	+	-	+	-	-	-	Na	Na	na	48 30 28	69,00%	25(1-142)
Tiberio 2016	105	1998-2013	68(57-74)	+	-	Na	-	Na	+	+	14.6%	12.4%(13)	82%	48 20 8	28,00%	na

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