

Hepatic metastases from gastric cancer: A surgical perspective

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Abstract

Management of patients with hepatic metastases as the sole metastatic site at diagnosis of gastric cancer (synchronous setting) or detected during follow-up (metachronous) is controversial. The prevailing attitude in these cases is passive, leading to surgical palliation and, possibly, to chemotherapy. Authors focused this editorial in order to promote a more pragmatic attitude. They stress the importance of recognizing the good candidates to curative surgery of both gastric cancer and hepatic metastases (synchronous setting) or hepatic disease alone (metachronous disease) from those who will not benefit from surgical therapy. In fact, in adequately selected subgroup of patients surgery, especially if integrated in multimodal therapeutic strategies, may achieve unexpected 5-year survival rates, ranging from 10% to 40%. The critical revision of the literature suggests that some simple clinical criteria exist that may be effectively employed in patients selection. These are mainly related to the gastric cancer (factors T, N, G) and to the extent of hepatic involvement (factor H). Upon these criteria it is possible to adequately select about 50% of cases. In the remaining 50% of cases a critical discussion on a case-by-case basis is recommended, considering that among these patients some potential long-survivors exist, that survival is strictly influenced by the ablation of the tumor bulk and by multimodality treatments including chemotherapy and that in expert institutions this kind of surgery is performed with very low mortality and morbidity rates.

Key words: Gastric cancer; Hepatic metastases; Therapeutic strategy; Selection criteria; Hepatectomy; Gastrectomy; Surgical palliation; Chemotherapy

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Core tip: Authors highlight the reasons for an active attitude in case of patients with gastric cancer and hepatic metastases. They show that when the liver is the sole metastatic site it is possible to select the good candidates for surgical management of both gastric cancer and hepatic metastases and to recognize those who will not benefit from an aggressive attitude. They also show that the multidisciplinary approach to these patients is the best option.

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Sparkling is research and clinical activity which focuses on hepatic metastases from colorectal cancer, but the waters surrounding hepatic metastases from gastric cancer are still.

In 2005 the French Association of Surgery^[1] produced the first report with more than 100 hepatectomies, recruiting 101 cases from 41 centres. In 2010 Kerkar *et al*^[2] reviewed 436 patients collected from 19 surgical series published over a 20-year time-span. The most recent review, published by Fitzgerald *et al*^[3] collected 481 cases published in the period 1990-2013. Despite this, the incidence of hepatic metastasis from gastric cancer during the course of the disease figures around 20% in eastern countries such as Japan and South Korea and rises to 30%-40% in Europe and North America, lying unmeasured -yet probably over 50%- in other less closely-monitored countries.

It seems that the clinical community does not include surgery among the therapeutic options for these patients. We all have daily experience of the aggressive biology of gastric cancer, especially when at metastatic stage. We also experience the frequent coexistence of multiple metastatic sites as well as hepatic involvement and are also aware that hepatic and systemic recurrence is almost systematically observed after hepatectomy or ablative treatments. However, literature is consistent in reporting unexpected results after aggressive multidisciplinary management including surgery in gastric cancer patients when the liver is the sole metastatic site^[4]. This clinical context is observed in about 33% of cases presenting hepatic metastases, but in these cases 5-year survival rate is reported between 10% and 40% of cases.

In other fields of our work, such as pancreatic cancer, surgeons struggle in their theatres for hours,

master difficult techniques, face perilous postoperative complications and accept surgical mortality for similar but often worse results. Why is this not the case for gastric cancer with hepatic metastases as the only metastatic site?

The main reason may be found in the curve that describes survival after surgery: a step drop is systematically observed during the first year, mortality is around 40% after 6 mo and reaches 70%-80% 1 year after surgery. This suggests the critical point: selection of candidates to curative surgery. All papers published on this topic investigate selection criteria and prognostic factors of major clinical relevance. However, thirteen of them^[5-16] are of great interest since their results are based on cohorts of patients as observed in every-day clinical practice and not upon super-selected populations submitted to surgical treatment.

In the different settings of the disease, synchronous and metachronous presentation, simple clinical variables such as factor T of gastric primary and extension H of hepatic involvement may be employed to select the best candidates for curative surgery^[6,7,10,15,16] and those to be excluded from hepatic resection. These factors also seem to display a cumulative effect. In the synchronous setting^[6] gastric cancer T > 2 and scattered bilobar metastases (H3) are negative prognostic factors with clear clinical value. In fact, median and 5-year survival was respectively 23 months and 27% for the 10% of cases which did not display the 2 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^[10] 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 mo. Upon these bases, it is possible to select the best candidates for curative resection, those for whom an aggressive treatment should be mandatory, from those who will not benefit from hepatectomy. All together, they represent 40%-55% of cases. In the middle one finds the huge group of cases presenting 1 risk factor. They do not display an astonishing survival performance (median survival is around 8-9 mo). Yet among these it is possible to find long-term survivors. We think that in these cases the therapeutic decision should be discussed on a case by case basis, considering that the major prognostic factor emerging from the cited papers is represented by the possibility to achieve a curative resection. This should be pursued whenever possible, also referring to ablative procedures such as RFA^[5,8]. It must be noted that in tertiary Institutions these complex procedures are safe: in both the synchronous and metachronous setting mortality is limited to some unit percent (0%-3%) and morbidity reflects that of major surgery,

well under 20% of cases.

We would like to stress here that the completeness of tumor bulk removal is a key-point of the therapeutic strategy. The expansion of the experience and the most recent series focusing on surgical subgroups^[1,17-25], indicate this point precisely. The importance of a radical resection/ablation of gastric cancer and hepatic metastases stands out progressively while other prognostic factors reveal themselves as disturbing and non-existent^[4].

A pragmatic multi-disciplinary approach, integrating neo-adjuvant and/or adjuvant chemotherapy, offers the possibility for further improvements in results. In our recent paper^[10], adjuvant chemotherapy revealed itself as the most powerful prognostic factor. The effective integration of the different disciplines will be the next breakthrough although it will require a great deal of hard work. Though a paradox, chemotherapy with neo-adjuvant intent is not routinely accepted in metastatic settings, especially in synchronous presentation, and patients are more often enrolled in protocols of palliative chemotherapy.

Concluding this editorial, we repeat that through slow but constant progress it is possible today to operate a certain selection of candidates to curative resection and that complete removal of the neoplastic bulk must be achieved. It is relatively easy to recognize the best candidates to be operated on or - at least - to be centralized in expert centres, where these complex procedures can be performed with very low operative morbidity and mortality. Upon this basis, we hope that a *μετάνοια* (change of mind) will spread through our community, leading to a general and consistent improvement of survival results, at least for some of the most unlucky among gastric cancer patients.

Will we accept the challenge?

REFERENCES

- 1 **Chiche L**, Ducreux M, Lebreton G. Métastases hépatiques des cancers de l'estomac. In: Adam R, Chiche L, editors. *Chirurgie des métastases hépatiques de cancers non colorectaux non endocrine*. Monographies de l'association Française de Chirurgie. Paris: Arnette, 2005: 45-59
- 2 **Kerkar SP**, Kemp CD, Avital I. Liver resections in metastatic gastric cancer. *HPB* (Oxford) 2010; **12**: 589-596 [PMID: 20961366 DOI: 10.1111/j.1477-2574.2010.00224.x]
- 3 **Fitzgerald TL**, Brinkley J, Banks S, Vohra N, Englert ZP, Zervos EE. The benefits of liver resection for non-colorectal, non-neuroendocrine liver metastases: a systematic review. *Langenbecks Arch Surg* 2014; **399**: 989-1000 [PMID: 25148767 DOI: 10.1007/s00423-014-1241-3]
- 4 **Gadde R**, Tamariz L, Hanna M, Avisar E, Livingstone A, Franceschi D, Yakoub D. Metastatic gastric cancer (MGC) patients: Can we improve survival by metastasectomy? A systematic review and meta-analysis. *J Surg Oncol* 2015; **112**: 38-45 [PMID: 26074130 DOI: 10.1002/jso.23945]
- 5 **Cheon SH**, Rha SY, Jeung HC, Im CK, Kim SH, Kim HR, Ahn JB, Roh JK, Noh SH, Chung HC. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. *Ann Oncol* 2008; **19**: 1146-1153 [PMID: 18304963 DOI: 10.1093/annonc/mdn026]
- 6 **Tiberio GA**, Coniglio A, Marchet A, Marrelli D, Giacomuzzi S, Baiocchi L, Roviello F, de Manzoni G, Nitti D, Giuliani SM. Metachronous hepatic metastases from gastric carcinoma: a multicentric survey. *Eur J Surg Oncol* 2009; **35**: 486-491 [PMID: 19171450 DOI: 10.1016/j.ejso.2008.12.017]
- 7 **Ueda K**, Iwahashi M, Nakamori M, Nakamura M, Naka T, Ishida K, Ojima T, Yamaue H. Analysis of the prognostic factors and evaluation of surgical treatment for synchronous liver metastases from gastric cancer. *Langenbecks Arch Surg* 2009; **394**: 647-653 [PMID: 18343941 DOI: 10.1007/s00423-008-0311-9]
- 8 **Hwang SE**, Yang DH, Kim CY. Prognostic factors for survival in patients with hepatic recurrence after curative resection of gastric cancer. *World J Surg* 2009; **33**: 1468-1472 [PMID: 19381718 DOI: 10.1007/s00268-009-0034-2]
- 9 **Makino H**, Kunisaki C, Izumisawa Y, Tokuhisa M, Oshima T, Nagano Y, Fujii S, Kimura J, Takagawa R, Kosaka T, Ono HA, Akiyama H, Tanaka K, Endo I. Indication for hepatic resection in the treatment of liver metastasis from gastric cancer. *Anticancer Res* 2010; **30**: 2367-2376 [PMID: 20651395]
- 10 **Tiberio GA**, Baiocchi GL, Morgagni P, Marrelli D, Marchet A, Cipollari C, Graziosi L, Ministrini S, Vittemberg G, Donini A, Nitti D, Roviello F, Coniglio A, de Manzoni G. Gastric cancer and synchronous hepatic metastases: is it possible to recognize candidates to R0 resection? *Ann Surg Oncol* 2015; **22**: 589-596 [PMID: 25190117 DOI: 10.1245/s10434-014-4018-6]
- 11 **Mohri Y**, Tanaka K, Ohi M, Saigusa S, Yasuda H, Toiyama Y, Araki T, Inoue Y, Kusunoki M. Identification of prognostic factors and surgical indications for metastatic gastric cancer. *BMC Cancer* 2014; **14**: 409 [PMID: 24906485 DOI: 10.1186/1471-2407-14-409]
- 12 **Yang SW**, Kim MG, Lee JH, Kwon SJ. Role of metastasectomy on overall survival of patients with metastatic gastric cancer. *J Gastric Cancer* 2013; **13**: 226-231 [PMID: 24511418 DOI: 10.5230/jgc.2013.13.4.226]
- 13 **Chen L**, Song MQ, Lin HZ, Hao LH, Jiang XJ, Li ZY, Chen YX. Chemotherapy and resection for gastric cancer with synchronous liver metastases. *World J Gastroenterol* 2013; **19**: 2097-2103 [PMID: 23599631 DOI: 10.3748/wjg.v19.i13.2097]
- 14 **Chen S**, Li YF, Feng XY, Zhou ZW, Yuan XH, Chen YB. Significance of palliative gastrectomy for late-stage gastric cancer patients. *J Surg Oncol* 2012; **106**: 862-871 [PMID: 22648960 DOI: 10.1002/jso.23158]
- 15 **Miki Y**, Fujitani K, Hirao M, Kurokawa Y, Mano M, Tsujie M, Miyamoto A, Nakamori S, Tsujinaka T. Significance of surgical treatment of liver metastases from gastric cancer. *Anticancer Res* 2012; **32**: 665-670 [PMID: 22287760]
- 16 **Liu J**, Li JH, Zhai RJ, Wei B, Shao MZ, Chen L. Predictive factors improving survival after gastric and hepatic surgical treatment in gastric cancer patients with synchronous liver metastases. *Chin Med J (Engl)* 2012; **125**: 165-171 [PMID: 22340539]
- 17 **Kim KH**, Lee KW, Baek SK, Chang HJ, Kim YJ, Park do J, Kim JH, Kim HH, Lee JS. Survival benefit of gastrectomy ± metastasectomy in patients with metastatic gastric cancer receiving chemotherapy. *Gastric Cancer* 2011; **14**: 130-138 [PMID: 21373855 DOI: 10.1007/s10120-011-0015-7]
- 18 **Ambiru S**, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Yoshidome H, Shimizu Y, Nakajima N. Benefits and limits of hepatic resection for gastric metastases. *Am J Surg* 2001; **181**: 279-283 [PMID: 11376587]
- 19 **Thelen A**, Jonas S, Benckert C, Lopez-Hänninen E, Neumann U, Rudolph B, Schumacher G, Neuhaus P. Liver resection for metastatic gastric cancer. *Eur J Surg Oncol* 2008; **34**: 1328-1334 [PMID: 18329229 DOI: 10.1016/j.ejso]
- 20 **Garancini M**, Uggeri F, Degrate L, Nespoli L, Gianotti L, Nespoli A, Uggeri F, Romano F. Surgical treatment of liver metastases of gastric cancer: is local treatment in a systemic disease worthwhile? *HPB* (Oxford) 2012; **14**: 209-215 [PMID: 22321040 DOI: 10.1111/j.1477-2574.2011.00428.x]
- 21 **Schildberg CW**, Croner R, Merkel S, Schellerer V, Müller V, Yedibela S, Hohenberger W, Peros G, Perrakis A. Outcome of operative therapy of hepatic metastatic stomach carcinoma: a

- retrospective analysis. *World J Surg* 2012; **36**: 872-878 [PMID: 22354489 DOI: 10.1007/s00268-012-1492-5]
- 22 **Takemura N**, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y, Hiki N, Sano T, Yamamoto J, Kokudo N, Yamaguchi T. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. *Langenbecks Arch Surg* 2012; **397**: 951-957 [PMID: 22615045 DOI: 10.1007/s00423-012-0959-z]
- 23 **Wang W**, Liang H, Zhang H, Wang X, Xue Q, Zhang R. Prognostic significance of radical surgical treatment for gastric cancer patients with synchronous liver metastases. *Med Oncol* 2014; **31**: 258 [PMID: 25260807 DOI: 10.1007/s12032-014-0258-3]
- 24 **Aizawa M**, Nashimoto A, Yabusaki H, Nakagawa S, Matsuki A. Clinical benefit of surgical management for gastric cancer with synchronous liver metastasis. *Hepatogastroenterology* 2014; **61**: 1439-1445 [PMID: 25513107]
- 25 **Liu Q**, Bi JJ, Tian YT, Feng Q, Zheng ZX, Wang Z. Outcome after simultaneous resection of gastric primary tumour and synchronous liver metastases: survival analysis of a single-center experience in China. *Asian Pac J Cancer Prev* 2015; **16**: 1665-1669 [PMID: 25743789]

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