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REVIEW ARTICLE

Liver resection for metastasis due to malignant mesenchymal tumours

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Abstract
While liver resection for colorectal metastases has shown promising long-term survival, data for metastasectomy in sarcoma and leiomyosarcoma patients have not yielded the same optimism. Due to the rarity of the tumour entity it has always been difficult to provide significant data. Advances in tumour classification suggest that most of the metastases formerly classified to be of sarcomatoid and especially leiomyosarcomatoid origin are actually metastases of GISTs (gastro-intestinal stromal tumours). Neoadjuvant/adjuvant imatinib therapy might improve overall survival and enable surgeons to provide resections in previously unresectable patients. Only R0 resection has been proven to prolong survival so far, with a long disease-free interval as the only independent predictor of outcome.

Key Words: *Sarcoma, leiomyosarcoma, GIST, metastasis, liver resection*

Introduction

Liver resection for metastatic disease has become one of the main pillars of interdisciplinary oncologic therapy in cancer patients. Through major advances in resection techniques and perioperative management even extended liver resection is now viewed as a safe procedure if performed at dedicated centres, with a mortality of $<5\%$ [1]. Good results with promising 5-year survival rates have been well documented for metastatic colorectal cancer in recent years [2,3].

Data for liver resection for metastatic sarcoma have not yielded the same optimistic standpoint so far – still it has been viewed as the best treatment option if an R0 resection is possible [4–6].

As the understanding of the diversity in tumour biology of sarcomas has dramatically changed over the past 5 years with the discovery of KIT tyrosine kinase and the definition of GISTs (gastro-intestinal stromal tumours) as an entity [7,8], one is led to rethink the available data in terms of realizing that most of the sarcomas and especially leiomyosarcomas described until recently are actually GISTs. Therefore, accounting for today's knowledge, indications for resection and patient survival might differ substantially from previous data if auxiliary treatment options like imatinib (STI571, Gleevac) are considered.

Pathology

The progress achieved in classifying primary and secondary sarcomas of the liver derives largely from the application of new methods in immunohistochemistry (antibodies, working on formalin-fixed and paraffin-embedded tissue) and molecular pathology, revealing specific genetic alterations. The vast majority of primary sarcomas of the liver are of angiogenic origin, i.e. angiosarcoma or epithelioid haemangioendothelioma.

Other primary sarcomas are very rare and suspected to represent metastasis of known or unknown origin, for instance in cases of late metastasis of low grade sarcomas [9].

GISTs and their metastases can be determined by expression of CD 117/c-kit or PDGF-alpha through immunohistochemistry [10].

An association between KIT exon 9 mutations and an intestinal origin of GISTs and between PDGFRA mutations and gastric origin of the tumours has been shown. Mutational status (in contrast to only amplification) was correlated with high risk/malignant GIST. Furthermore, the morphological phenotype is correlated with specific mutations [11]. A striking difference in gene expression between stomach and small bowel GISTs has already been shown by gene

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array examination [12], explaining their variable behaviour and response to therapy.

An up to date classification of secondary liver sarcomas should include the examination of the expression status for c-Kit/Cd-117 and PDGF-alpha using immunohistochemistry. As not only immunohistochemistry but also extraction of suitable DNA from paraffin-embedded archival tissue is practicable [13], a retrospective reclassification by immunohistochemistry and molecular pathology of already published larger series of secondary malignant mesenchymal tumours should be achieved to obtain the real rate of GISTs in hepatic metastasis and a better correlation with clinical data, especially survival rates.

Liver resection

The available data for these tumour entities are limited. Considering the new classification for sarcomas it is important to keep in mind that nearly all available data are derived from collections of patients that were not identified by applying those new classifications.

Additionally, most data concern calculated survival rates for patient collections including all kinds of non-colorectal, non-neuroendocrine (NCNNE) tumours – therefore it is difficult to extract data for sarcomas, especially if the new definitions are applied.

Table I provides an overview of studies for NCNNE tumours including sarcoma. Table II shows the data from series that focused on sarcomas but did not differentiate GISTs as an entity. The tables include the estimated amount of GIST cases as extracted from the data where possible.

Liver resection itself is considered a safe procedure nowadays [1] and it is still the only treatment available with the possible chance of a cure for metastatic disease. Therefore aggressive attempts at R0 resection are justified [6,14,15]. New strategies like portal embolization aimed at inducing hypertrophy of tumour-free parenchyma allow even more extensive resections.

Discussion

Liver resection for metastatic disease of colorectal cancer has been widely established as a safe procedure and promising curative approach. Even second and third resections after tumour recurrence have shown acceptable results with an overall 5-year survival of up to 40% [1–3].

Unfortunately the data for metastasis of sarcoma and leiomyosarcoma are not that clear. Only one larger series concerning hepatic metastases from leiomyosarcoma [6] and one for metastatic sarcoma [15] are available at present, while other publications describe only few cases [8,14,16–18]. As the tumour entity is rather rare the described cases are usually published as part of series of NCNNE tumours [4,5,19–21].

Considering the rather recent advances in pathologic definitions of sarcomas it could be well argued that the published series are not up to date, as the new classification and diagnostic tools concerning sarcomas were not available at the time of publication [7,22,23]. DeMatteo found that 40% of all patients treated for metastatic sarcoma actually had GISTs [15]. Nevertheless, the results of all published series have established an improved survival after R0 resection of roughly 30 months and a possible 5-year survival rate of 20%, slightly favouring metastases of sarcomas over leiomyosarcomas compared with non-operative treatment. Without treatment the median survival of patients is <14 months, while chemotherapy and chemoembolization usually provide poor response rates and a median duration of regression for 12 months [5].

The key to success is patient selection. The poor results for patients with R1/R2 resections, especially in face of extrahepatic tumour masses, are still better than the results accomplished with chemotherapy or chemoembolization but nevertheless are poor, with a median survival of 20 months. This justifies an aggressive attempt at R0 resection considering extended hepatectomies and even extracorporeal liver resections [6,14]. Patients have to be evaluated carefully before any surgical attempt is made, focusing on the existence of extrahepatic tumour and possible liver

Table I. Studies of liver resection with metastasis due to NCNNE tumours.*

Group	Centre	Number of cases	SC/LMSC cases	Supposedly GISTs	1-year survival	3-year survival	5-year survival
Ercolani et al. 2004	Bologna, Italy	83	10	10	75%	63%	36%
Karavias et al. 2002	Patras, Greece	18	4	4	Not recorded	3 alive after 2 years	1 alive after 4 years
Kalil et al. 1999	Porto Alegre, Brazil	5	5	4	100%	75%	0%
Harrison et al. 1997	New York, USA	96	27	14	Not recorded	Not recorded	26%

GIST, gastrointestinal stromal tumour; LMSC, leiomyosarcoma; NCNNE, non-colorectal, non-neuroendocrine; SC, sarcoma.
*Sarcoma and leiomyosarcoma cases account for a small number of tumours in these studies. GISTs have not been identified separately. The likely amount of GISTs in the series are mentioned in the 'supposedly GISTs' section of the table. The survival rates display results for the concerned subgroups.

Table II. Studies of liver resection with metastasis due to sarcoma and leiomyosarcoma.

Group	Centre	Number of cases	R0 resection	Supposedly GISTs	1-year survival	3-year survival	5-year survival	Recurrence
DeMatteo et al. 2001	New York, USA	331	56	34 (61%)	88%	50%	30%	47 (84%)
Lang et al. 1999	Hannover, Germany	34	15	4	Not recorded	Not recorded	20%	9 (60%)
Chen et al. 1998	Baltimore, USA	11	6	5	Not recorded	4	Not recorded	3

The likely amount of GISTs in the series is mentioned in the 'supposedly GISTs' section. Survival data are for patients with R0 resection. R0 is defined as resection with microscopically tumour-free margins. The 'Recurrence' section represents tumour recurrence despite R0 resection.

resection. Induction of hypertrophy through portal vein embolization might be feasible in cases where a resection would be otherwise limited due to a small liver remnant [24]. A second liver resection for tumour recurrence suggests benefits in terms of survival [6], but long-term survival in this group of patients has not been reported yet. It is reasonable to speculate that most of the lesions formerly called sarcomas and leiomyosarcomas in previous studies would be classified as GISTs nowadays. Considering the rather promising results of medical treatment with imatinib it seems reasonable to think about neoadjuvant and adjuvant approaches in these patients. Some cases have already been reported [8,25].

In one case report even interventional arterial embolization after surgery was effective [18]. Tepetes et al. reported a case in which adjuvant chemotherapy and radiofrequency ablation were successful, although in this case the test for cKit was negative [17]. Two studies concerning the adjuvant and neoadjuvant effects of imatinib are being conducted at present, unfortunately the results are pending at the time of writing [26,27]. Keeping in mind the high rate of recurrent disease even after R0 resection [6,14,15], these studies are very important. (see also Table II). Debulking operations have not shown significant survival benefit yet [6,15,25], but this could change if a neoadjuvant/adjuvant treatment would allow a R0 resection.

Liver resection itself has been shown to prolong survival; this seems especially true for patients with small metastasis and a long disease-free interval. A time to metastasis of >2 years has actually been an independent predictor of outcome in a large group of patients published by DeMatteo et al. [15], with a median survival of 61 months.

Conclusion

Liver resection still provides the only possible cure for metastatic disease of sarcoma. Extensive resections using the whole arsenal of modern tools are justified, as only an R0 resection provides the chance for long-term survival. GISTs are likely to account for the largest group of metastases discovered; therefore preoperative staging including immunohistochemical examination of acquired specimens is necessary whenever possible. There are not enough data to support neoadjuvant/adjuvant treatment in metastatic disease, but the high recurrence rate after surgery is evident. Nevertheless, the promising data for primary GISTs under imatinib therapy suggest the possibility for preoperative down-staging and improved overall survival.

References

[1] Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg 1995;19:59–71.

[2] Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000;231: 487–99.

[3] Schlag P, Hohenberger P, Herfarth C. Resection of liver metastases in colorectal cancer – competitive analysis of treatment results in synchronous versus metachronous metastases. Eur J Surg Oncol 1990;16:360–5.

[4] Ercolani G, Grazi GL, Ravaioli M, Ramacciato G, Cescon M, Varotti G, et al. The role of liver resections for noncolorectal, nonneuroendocrine metastases: experience with 142 observed cases. Ann Surg Oncol 2005;12:459–66.

[5] Karavias DD, Tepetes K, Karatzas T, Felekouras E, Androulakis J. Liver resection for metastatic non-colorectal non-neuroendocrine hepatic neoplasms. Eur J Surg Oncol 2002; 28:135–9.

[6] Lang H, Nussbaum KT, Kaudel P, Fruhauf N, Flemming P, Raab R. Hepatic metastases from leiomyosarcoma: a single-center experience with 34 liver resections during a 15-year period. Ann Surg 2000;231:500–5.

[7] Heinrich MC, Corless CL. Gastric GI stromal tumors (GISTs): the role of surgery in the era of targeted therapy. J Surg Oncol 2005;90:195–207; discussion 207.

[8] Okamoto K, Muguruma N, Aoki R, Sato Y, Nakamoto J, Imoto Y, et al. A treatment using STI571 for jejunal gastrointestinal stromal tumor (GIST) accompanied with liver metastasis and peritoneal dissemination. Intern Med 2004;43: 1151–6.

[9] Flemming P, Wellmann A, Maschek H, Lang H, Georgii A. Monoclonal antibodies against inhibin represent key markers of adult granulosa cell tumors of the ovary even in their metastases. A report of three cases with late metastasis, being previously misinterpreted as hemangiopericytoma. Am J Surg Pathol 1995;19:927–33.

[10] Rossi G, Valli R, Bertolini F, Marchioni A, Cavazza A, Mucciarini C, et al. PDGFR expression in differential diagnosis between KIT-negative gastrointestinal stromal tumours and other primary soft-tissue tumours of the gastrointestinal tract. Histopathology 2005;46:522–31.

[11] Penzel R, Aulmann S, Moock M, Schwarzbach M, Rieker RJ, Mechtersheimer G. The location of KIT and PDGFRA gene

mutations in gastrointestinal stromal tumours is site and phenotype associated. J Clin Pathol 2005;58:634–9.

[12] Antonescu CR, Viale A, Sarran L, Tschernyavsky SJ, Gonen M, Segal NH, et al. Gene expression in gastrointestinal stromal tumors is distinguished by KIT genotype and anatomic site. Clin Cancer Res 2004;10:3282–90.

[13] Lehmann U, Kreipe H. Real-time PCR analysis of DNA and RNA extracted from formalin-fixed and paraffin-embedded biopsies. Methods 2001;25:409–18.

[14] Chen H, Pruitt A, Nicol TL, Gorgulu S, Choti MA. Complete hepatic resection of metastases from leiomyosarcoma prolongs survival. J Gastrointest Surg 1998;2:151–5.

[15] DeMatteo RP, Shah A, Fong Y, Jarnagin WR, Blumgart LH, Brennan MF. Results of hepatic resection for sarcoma metastatic to liver. Ann Surg 2001;234:540–7; discussion 547–8.

[16] Kalil AN, de Lourdes Pereira B, Brenner MC, Pereira-Lima L. Liver resections for metastases from intraabdominal leiomyosarcoma. HPB Surg 1999;11:261–4.

[17] Tepetes K, Tsamandas AC, Ravazoula P, Petsas T, Bonikos DS, Karavias DD. Survival for 5 years after repeat liver resections and multimodality treatment for metastatic intestinal leiomyosarcoma: report of a case. Surg Today 2002;32: 925–8.

[18] Hara T, Wada I, Kajihara S, Mizuta T, Yamamoto K, Sakai T. Case report: a long-term survivor of jejunal leiomyosarcoma with liver metastasis: effective transcathetel arterial embolization for hepatic metastatic foci. J Gastroenterol Hepatol 1998; 13:620–3.

[19] Harrison LE, Brennan MF, Newman E, Fortner JG, Picardo A, Blumgart LH, et al. Hepatic resection for noncolorectal, nonneuroendocrine metastases: a fifteen-year experience with ninety-six patients. Surgery 1997;121:625–32.

[20] Hemming AW, Sielaff TD, Gallinger S, Cattral MS, Taylor BR, Greig PD, et al. Hepatic resection of noncolorectal nonneuroendocrine metastases. Liver Transpl 2000;6: 97–101.

[21] Weitz J, Blumgart LH, Fong Y, Jarnagin WR, D'Angelica M, Harrison LE, et al. Partial hepatectomy for metastases from noncolorectal, nonneuroendocrine carcinoma. Ann Surg 2005;241:269–76.

[22] Logrono R, Jones DV, Faruqi S, Bhutani MS. Recent advances in cell biology, diagnosis, and therapy of gastrointestinal stromal tumor (GIST). Cancer Biol Ther 2004;3: 251–8.

[23] Nowain A, Bhakta H, Pais S, Kanel G, Verma S. Gastrointestinal stromal tumors: clinical profile, pathogenesis, treatment strategies and prognosis. J Gastroenterol Hepatol 2005; 20:818–24.

[24] Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. Br J Surg 2001;88: 165–75.

[25] Rutkowski P, Nyckowski P, Grzesiakowska U, Nowecki ZI, Nasierowska-Guttmejer A, Pienkowski A, et al. The clinical characteristics and the role of surgery and imatinib treatment in patients with liver metastases from c-Kit positive gastrointestinal stromal tumors (GIST). Neoplasma 2003;50: 438–42.

[26] http://www.rotg.org/ (2005) Internet communication.

[27] https://www.acosog.org/studies/closed.jsp (2005) Internet communication.