REVIEWS

Metastatic lesions to the liver: Surgical indications and techniques

Luis Tejedor[1], Alejandro Serrablo[2]

1. General Surgery Department, Punta Europa Hospital, Algeciras, Spain. 2. HPB Surgical Unit, Miguel Servet University Hospital, Zaragoza, Spain.

Correspondence: Alejandro Serrablo. Address: HPB Surgical Unit, Miguel Servet University Hospital, Zaragoza, Spain. Email: almaley@telefonica.net

Abstract

Background: Although there is an established agreement on the advantage of liver resection for metastatic colorectal and neuroendocrine tumours, the role of hepatic surgery in patients with liver metastases from non-colorectal and non-neuroendocrine carcinoma is not well defined. In recent years, despite the poor results, liver metastases suitable for surgery have been treated with resection. The results reported in recent studies support a developing trend toward surgery in this setting. Also, as there are no data that in fact suggest the utility of alternative treatments for these lesions, the role of surgery is reinforced.

Methods: A systematic search of English and non-English literature using MEDLINE on the outcomes of patients after surgical treatment of liver metastases from different solid tumours was undertaken. A summary of current surgical techniques used to improve their resectability has been added.

Results: All papers reporting median survival and 5-year survival have been selected and presented in tables for most of the primary tumours reviewed.

Conclusions: Apart from patients with colorectal and neuroendocrine tumours, liver resection may offer a significative survival advantage in selected patients, mainly those with metastases coming from breast, gastrointestinal stromal tumours, testis, ovary and kidney.

Key words

Liver metastases, Surgery for liver metastases, Liver resection techniques

1 Introduction

Surgery is clearly indicated for treatment of liver metastases from colorectal and neuroendocrine tumours but it's not plainly established for metastases from others primaries, since survival results after liver resection of these later cases have been uniformly poor. However, during the last decade a valuable number of reports showed better survival after this surgery, so that a rethinking on the management of these conditions is considered worthwhile.

We carried out a systematic search of papers reporting survival outcomes of these patients after hepatic resection, trying to clarify the surgical indications for these lesions. Unfortunately, but also as expected, most of the reports are retrospective, include a short number of patients, and the biases in the selection of its patients are difficult to estimate.

2 Surgical indications in metastatic lesions to the liver

2.1 Colorectal cancer

The liver is the organ most frequently involved and often the sole site of metastasis in colorectal cancer. In 20%-25% of the patients colorectal liver metastases (CLM) are present at the time of diagnosis while around 40% of the patients are diagnosed after resection of the primary tumour [1]. CLM are limited to one lobe in less than one third of patients and are solitary lesions in only 10% of cases.

Without treatment, median survival is less than eight months. Survival with untreated CLM at five years is unusual (0-3%) but increases to 35%-58% after resection with curative intent [2]. Hepatic resection offers the only chance of long-term survival for patients with CLM. The first large series concluding that there is a benefit for surgery in selected patients with CLM was reported in 1978 [3]. The 5-year survival rate for these patients has increased from about 30% two decades ago to nearly 60% nowadays, with a 10-year overall survival of 20%-25% for radically resected patients [4] (Table 1).

Table 1. Liver resections for CLM

Author	Year	N patients	Median survival	5-year survival
Minagawa [5]	2000	235	-	38
Bolton [6]	2000	165	-	36
Figueras [7]	2001	235	51 mo	36
Choti [8]	2002	133	46 mo	58
Okano [9]	2002	152	-	67
Abdalla [10]	2004	190	-	58
Fernandez [11]	2004	100	22 mo disease-free	58
Pawlik [12]	2005	557	> 49 mo	58
Wei [13]	2006	423	53 mo	47
Shah [14]	2007	841	48 mo	43
Tanaka [15]	2008	277	-	45
Rees [16]	2008	929	42 mo	36
De Jong [17]	2009	1669	36 mo	47
Morris [18]	2010	3116	-	44

Surgery is becoming safer (operative mortality rate is less than 1%) and new systemic therapies increase patient survival. Some strategies may increase the amount of liver remaining after resection. The old criteria for resectability have been surpassed, expanding the indications for resection.

Although all patients with CLM are classified as having stage IV disease in the TNM classification of liver tumours, they form a very heterogeneous group (synchronous and metachronous metastases, node-positive and node-negative disease, unilobar and bilobar lesions, and extrahepatic or no extrahepatic disease) with a very variable prognosis. For example, the survival for a patient with a solitary, resectable liver metastasis is better than that for a patient with stage III disease. Several clinical scores attempt to predict more accurately the outcome of these patients [19-23], but their validation is still

limited. One more recent proposal from the European Colorectal Metastases Treatment Group defines stage IV colorectal cancer as a tumour spreading beyond N2 lymph node status of the primary with added liver-only disease. It is further stratified as A (easily resectable liver metastases), B (resectable liver metastases), C (liver metastases that may become resectable after downsizing) and D (liver metastases that are unlikely to become resectable) depending on treatment approach and prognosis. Furthermore, a stage V, A and B, refers to resectable and unresectable disease, respectively, outside of the liver [24]. Currently, restratification, particularly the grid staging system [25], is based on the resectability of hepatic and extrahepatic metastases.

2.2 Neuroendocrine tumours

Gastrointestinal neuroendocrine tumours (NETs), either carcinoid or pancreatic histological subtypes, originate throughout the gastrointestinal tract. They show a relatively slow rate of growth and the potential to produce a variety of hormones. NETs of pancreatic origin can be non-functioning or can produce hormonally active substances such as insulin, gastrin, vasoactive intestinal peptide and others. Carcinoid tumours arise commonly in the midgut and may secret serotonin and other bioactive amines.

Almost 10% of all liver metastases are neuroendocrine in origin. Liver is the most common organ involved, followed by bone and lung [26]. Most of patients will have disseminated disease at the time of diagnosis and a 5-year survival between 50% and 80%. Liver metastases of NETs (LMNETs) occur in 50% to 75% of small-bowel carcinoids, in 5% to 70% of foregut carcinoids and in 14% of hindgut carcinoids. In many patients this is the only site of metastatic disease for a prolonged period of time. LMNETs are usually multifocal, bilobars and involve more than 50% of the liver parenchyma in more than half of the cases [27], but hepatic resection achieves an almost doubled 5-year survival rate compared with the non-resected patients (47%-82% *vs.* 30%-40%, respectively) [28].

There is not a firm consensus on the optimal treatment strategy of LMNETs, although some guides have been published [29, 30]

Table 2. 2007 Consensus guidelines for the treatment of liver metastases from neuroendocrine tumours

Liver metastasis for NETs	Management
LMNET without extrahepatic disease	Surgical resection of both primary and all liver metastasis ± local ablative techniques If unresectable or poor surgical candidate: continued biotherapy, hepatic artery chemoembolization (TACE) or embolization and radiofrequency ablation (RFA) Liver transplantation considered in rare cases

LMNET with extrahepatic disease	Biotherapy or other systemic nonsurgical treatment
	Palliative treatment if symptoms progress
	   If small number of isolated liver metastases less than 3cm-4 cm: RFA, TACE or embolization; may consider minor or anatomic resection in selected cases.
	   If complex (bilobar) pattern of liver metastases: RFA, or embolization; may consider major liver resection together with RFA for selected cases.
	   If diffuse pattern of liver metastases: TACE or embolization.

Several studies have shown 5-year survival rates of up to 86% in R0 resection for both primary and secondary sites (Table 3). Cytoreduction is useful as a palliative approach but it needs to reach at least 90% of tumour volume reduction to improve both survival and symptoms [31].

Normalization of tumour markers after surgery, 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A, predict a complete resection. When radiofrequency ablation (RFA) is the only treatment, relief of symptoms is obtained in 60% of the cases and local control in 80%, although the length of response is short. Transarterial chemoembolization (TACE), contraindicated when the tumour size exceeds 50% of the liver due to the risk of liver failure, also has a short duration of response. There is also a risk of causing carcinoid tumour lysis syndrome or crises.

Table 3. Liver resection for neuroendocrine liver metastases

Author	Year	N patients	% free of symptoms	5-year survival
Yao [32]	2001	16	-	70
Coppa [33]	2001	20	-	67
Jaeck [34]	2001	13	100	68
Nave [35]	2001	31	-	86
Sarmiento [31]	2003	170	96	61
Knox [36]	2003	13	82	85
Touzios [27]	2005	19	95	72
Musunuru [37]	2006	13	100	83
Norton [38]	2003	16	100	82
Elias [39]	2003	47	-	71
Osborne [40]	2006	61	91	80
Hibi [41]	2006	21	100	41
Gomez [42]	2007	18	100	86
Landry [43]	2008	23	-	75
Chambers [44]	2008	30	86	74
Ahmed [45]	2009	50	-	74

The role of liver transplantation in patients with LMNETs remains controversial, especially given the shortage of donors. Few liver transplants have been performed for LMNETs (less than 1% of the total) and, outside of a few small studies, survival does not seem to have improved. Frilling et al suggests some criteria for transplantation of these patients: age younger than 65, primary tumour under control, absence of extrahepatic disease proven over a 6-month period, progression of liver tumours and excessive hormonal symptoms refractory to medical therapy [46].

Although long-term cure can only be achieved in a small proportion of patients with malignant NETs, significant long-term palliation can be achieved. An aggressive surgical approach may also lead to long-term survival in these patients.

2.3 Non-colorectal non-neuroendocrine tumours

After colorectal origin, pancreas, breast, ovary and stomach are the following sources of liver metastasis in decreasing order of frequency [47]. The usefulness of liver resection seems clear for metastatic colorectal and neuroendocrine tumours but is much less apparent for non-colorectal non-neuroendocrine (NCRNNE) carcinoma. Many reasons support this insight. Most reported series are not comparable in terms of mid- and long-term (tumour-free) survival, as they include patients with NCRNNE hepatic metastases from different primary malignancies, different frequency of isolated hepatic metastases, different tumoral behaviour, and different sensitivity to chemotherapy and different length of disease-free interval between the resection of the primary tumour and the diagnosis of the liver metastases. In addition, many studies

include recruitment periods of 10 years or more so the chemotherapy scheme has substantially changed. The conclusions are that prognostic factors for liver metastases from NCRNNE should be taken with caution.

Before surgery, disease-free interval from the primary tumour must be considered. Twelve months is considered as generic minimum period between primary tumour and secondary disease to give an indication for surgery for liver metastases. After this first year, any further time interval should be considered as a progressively increasing positive prognostic factor. A longer disease-free interval is believed to indicate less aggressive tumour biology or a lower account of tumoral stem-cells [48].

In a retrospective study of 1452 patients treated at 41 centres, Adam et al demonstrated that liver resection for NCRNNE hepatic metastases is safe and effective. The authors categorized the outcome according to the primary tumour and the 5-year survival after liver resection into: favourable (adrenal, testicular, ovarian, small bowel, ampullary, breast, renal, and uterine tumours); intermediate (gastric adenocarcinoma, exocrine pancreas, cutaneous melanoma, choroidal melanoma, and duodenal tumours); and poor (gastroesophageal junction, pulmonary, esophageal, and head and neck tumours) [49] (Table 4).

Table 4. Liver resection for NCNNE liver metastases

Author	Year	N patients	5-year survival
Harrison [50]	1997	96	37
Hemming [51]	2000	37	45
Laurent [52]	2001	39	35
Yamada [53]	2001	33	12.1
Cordera [54]	2005	64	30
Ercolani [55]	2005	142	34.3
Adam [49]	2006	1452	36
Lendoire [56]	2007	106	19
Reddy [57]	2007	360	37
O'Rourke [58]	2008	102	39
Lehner [59]	2009	242	28
Marudanayagam [60]	2011	65	25.6
Groeschl [61]	2012	420	31

Liver resection for NCRNNE liver metastases is still a matter of discussion because only small studies have been carried out in this field and the conclusive outcomes are collective and not specific for each type of tumour. Despite this, some series show long-term outcomes after resection, nearly equivalent to those of colorectal tumours.

2.3.1 Gastrointestinal stromal tumours

Gastrointestinal stromal tumours (GIST), the most common mesenchymal neoplasms of the gastrointestinal tract, are thought to come from intestinal pacemaker cells, also known as interstitial cells of Cajal [62, 63], and account for 1%-3% of all gastrointestinal malignancies [64]. They affect mostly males between the ages of 50 and 70, and are usually found incidentally at early stages. They also show a broad spectrum of biological behaviours, from indolent to rapidly progressive malignancies [65]. Large or advanced lesions may present with a variety of clinical findings, including bleeding, abdominal pain, early satiety, bowel obstruction or perforation.

The only definitive treatment for GIST is surgical resection. At presentation, approximately half of these tumours have already metastasized. The liver is the most frequent site of metastases and liver metastases are a major determinant of survival. Up to 55%-72% of patients develop hepatic metastasis following complete resection of the primary tumour [66]. Treatment includes anthracycline and ifosfamide-based chemotherapy regimes, TACE, surgical resection and hepatic transplantation, but high recurrence rates and poor survival outcomes following hepatic transplantation have been reported. Radical surgical resection, including hepatectomy, is the only potential treatment modality for this clinical condition. Liver resection itself has been shown to prolong survival, especially 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 with a median survival of 61 months [67].

Imatinib mesylate (Glivec®), a tyrosine kinase inhibitor (TKI), has revolutionized the management of this disease. Imatinib has a significant shrinking effect on GIST and can be used when primary GIST have attained a very large size or are in unfavourable locations, increasing the risk of positive resection margins [68]. Imatinib has also become the first line of treatment for recurrent and/or metastatic GIST. Another TKI, sunitinib, achieves responses in imatinib-refractory GISTs. Before the advent of TKIs surgical resection was the primary treatment for hepatic gastrointestinal stromal tumour (GIST) metastases. Although TKIs have improved survival in the metastatic setting, outcomes after multimodal therapy comprised of hepatectomy and TKIs for GIST are unknown. A recent report concludes that this combination therapy is more effective than surgery or TKI therapy alone [69]. Resection of GIST liver metastases may be curative when the primary disease has been eradicated and negative surgical resection margins are attained (Table 5).

Table 5. Liver resection for GIST, sarcomas and leiomyosarcomas liver metastases

Author	Year	N patients	Median survival	5-year survival
Chen [70]	1998	6	39	NR
Lang [71]	2000	18	28	13
Shima [72]	2003	10	39	11 (disease-free)
Nunobe [73]	2005	18	36	34
Paulik [74]	2006	36	47	27
Gomez [65]	2007	11	NR	91

In summary, surgical resection with curative intent should be considered when feasible, as it may improve survival outcomes in selected patients. Recurrence of disease can be managed with further surgery, RFA, imatinib mesylate therapy or a combination of these treatment modalities.

2.3.2 Breast cancer

Visceral metastases from breast cancer have an unlucky prognosis. Liver metastases are uncommon as the sole site of systemic disease: only 3% to 11% of patients have the liver as the single involved organ out of 65% of breast cancer patients with liver metastases as part of the disseminated disease [75], and even rarer is a solitary metastasis. Around 60% of responses can be obtained with systemic treatment but long-term survival is unusual, varying from 1 to 15 months [76]. Moreover, around 70% of these liver metastases are negative for hormonal receptors so that chemotherapy is usually the only treatment.

Extrahepatic disease has been considered as a contraindication for liver resection in these patients, but some reports have not found differences in survival between operated patients with or without extrahepatic breast cancer metastases, bearing in mind that most of the these extrahepatic lesions were bone metastases treated with chemotherapy and radiotherapy previously to surgery [77]. Other retrospective study of 454 patients operated on for metastatic breast cancer reported that 41% and 21% of these patients remain alive at 5 and 10 years, respectively [49]. Some series of liver resection for breast

cancer are shown in Table 6. Differences in outcome among series may merely reflect difference in selection criteria and in tumour biology.

Table 6. Liver resection for breast cancer liver metastases

Author	Year	N patients	Median survival	5-year survival
Santoro [78]	2000	15	NR	38
Yoshimoto [79]	2000	25	34 mo	27
Selzner [80]	2000	17	24 mo	40
Maksan [81]	2000	20	NR	36
Krisat [82]	2000	45	NR	36
Pocard [83]	2001	65	41 mo	46
Carlini [84]	2002	17	53 mo	46
Elias [85]	2003	54	34 mo	34
Vlastos [86]	2004	31	63 mo	61
Sakamoto [87]	2005	34	36 mo	16
Ercolani [88]	2005	21	42 mo	25
D'Annibale [89]	2005	18	32 mo	30
Adam [49]	2006	454	45 mo	41
Thelen [90]	2008	39	NR	42
Caralt [91]	2008	12	36 mo	33

Resection criteria for liver metastases from breast cancer are not yet clearly defined. Response to chemotherapy appears to be an important predictor of survival following hepatic resection. In Adam`s report, patients who remained stable or progressed on prehepatectomy chemotherapy were 3.5 times more likely to die than responders. Indeed, preoperative chemotherapy is a modality to prolong survival and the response can be considered as a selection criteria.

Two prognostic factors have been identified by several authors [83]: prolonged tumour-free interval (1-2 years) between breast cancer surgery and liver metastases diagnosis and no lymph node involvement at the time of breast cancer. Liver surgery should be offered to every patient with a good performance status, with predictable R0 resection and with a long disease-free interval (Figure 1).

In synchronous tumours, disease must be stabilized with chemotherapy. To consider surgery, there should not be extrahepatic disease or it must be a solitary bone metastasis. Surgery can be technically hampered because of the effects of chemotherapy on liver parenchyma. Hilar lymphadenectomy can be considered since positive lymph nodes are frequent, although they do not exclude resection.

Liver recurrence is very high and the best chemotherapy regimen in these cases is to be defined. Survival after resection is longer compared with other treatments, although disease-free time is usually brief.

Some authors suggest that liver resection in highly selected patients may function as a cytoreductive rather than a curative procedure, because breast liver metastasis is considered as a disseminated disease, and as a cytoreductive approach it improves the survival rate.
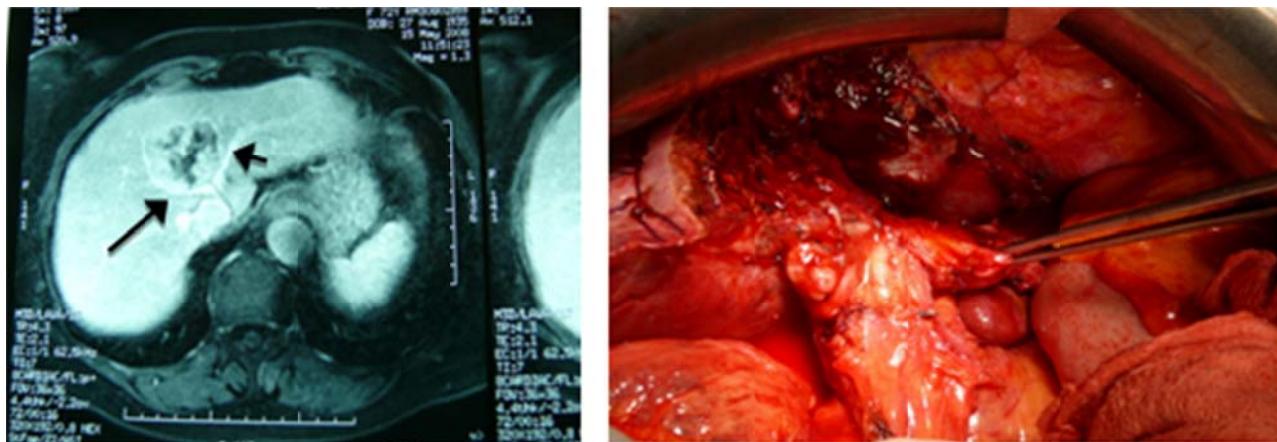
Figure 1. 71 years old woman with a solitary liver metastasis that involved middle (arrow) and left (arrow head) hepatic veins. Sg 2,3,4,5 and 8 have been removed. She is disease-free 5 years after liver resection.

2.3.3 Melanoma

Up to 30% of patients with melanoma develop distant metastases. After lungs and brain, liver is the third most involved organ. Previously considered an infrequent condition, autopsy studies have shown liver metastases in 55%-75% of the patients with melanoma [92, 93]. Mean survival after diagnosis ranges between 2 and 6 months. Single metastases are rare. Diagnosis is generally made by imaging studies during follow-up, since symptoms are suggestive of advanced disease. FDG PET/CT shows a sensitivity of 85%, a specificity of 100% and a positive predictive value of 98% [94]. Median survival in these patients ranges between 2 and 6 months [95]. Palliative radiotherapy and systemic chemotherapy do not prolong survival and, although interferon-α and interleukin-2 have yielded promising response rates, they are rarely durable [96]. New drugs such as vemurafenib, a BRAF kinase inhibitor, seem to achieve longer responses.

Table 7. Liver resection for melanoma liver metastases

Author	Year	N patients	Median survival (months)	5-year survival
Rose [93]	2001	24	28	29
Wood [100]	2001	15	14	20
Hsueh [101]	2004	24 ocular	11	7
Pawlik [98]	2006	16 ocular 24 cutaneous	26 NR	20 0
Crook [102]	2006	5	NR	60
Adam [49]	2006	44 cutaneous 104 ocular	NR	22 21
Herman [103]	2007	10	22	NR
Chua [104]	2010	13	21	40 (3 years)

A reduction in immunosuppressive factors and a slowing of the growth of occult metastases have been proposed as part of the beneficial effects of liver resection [97] (Table 7). A large series reports a 21% 5-year survival rate for 104 patients after resection of liver metastases from melanoma of choroidal origin and a 22% 5-year survival rate for 44 patients with the same condition but with a cutaneous source [49]. The same paper confirmed that choroid melanomas were commonly associated with multiple intrahepatic tumours but were less likely than cutaneous melanomas to be associated with extrahepatic disease. A series collected from four centres showed that the location of the primary tumour substantially

impacts on the recurrence and survival after resection of secondary liver tumours. Among 40 patients who underwent liver resection, the rate of recurrent hepatic metastases was higher among patients with ocular (53.3%) compared to those with cutaneous tumours (17.4%) [98].

Positive prognostic factors are R0 resection, solitary metastasis and absence of extrahepatic disease [99]. Resection with negative margins offers the only chance of long-term survival, since for R1 and R2 resection there are not periods of survival longer than 6 months.

For all the authors, liver resection must not be considered as a curative treatment but as a part of the whole oncologic treatment because of its cytoreductive nature. Reported series during the last decade show that liver resection of metastases from melanoma are infrequent, that the interval between treatment of primary and secondary tumour is long (49 to 96 months), that major hepatectomies are performed in 50% to 60% of the patients and that survival varies widely, which indicates that this is a very heterogeneous group of patients with a very variable criteria for resection.

2.3.4 Gastric cancer and others non-colorectal gastrointestinal adenocarcinoma

Many reports defend liver resection for metastatic gastric cancer although the indications for resection have not been established. Frequently, liver metastases suggest an advance disease with a mean survival of less than 6 month. Recent studies showed increased survival benefit with 5-year survivors between 20% and 60% (Table 8).

Table 8. Liver resection for gastric cancer liver metastases

Author	Year	N patients	Median survival	5-year survival
Ambiru [105]	2001	40	12	18
Fujii [106]	2001	10	16	10
Imamura [107]	2001	17		0
Zacheri [108]	2002	15	9	0
Saiura [109]	2002	10	25	20
Okano [110]	2002	19	21	34
Shirabe [111]	2003	36	NR	26
Roh [112]	2005	11	19	18
Adam [49]	2006	64	15	27
Hirai [113]	2006	14	NR	42
Sakamoto [114]	2007	37	31	11
Koga [115]	2007	42	34	42
Thelen [116]	2008	24	NR	15
Cheon [117]	2008	22	17	23
Morise [118]	2008	18	13	27
Ueda [119]	2009	15	NR	60

Positive prognostic factors have been identified: solitary tumour or not more than 3 nodules, size less than 5 cm, unilobar distribution, resection margin more than 10 mm and disease-free interval between gastric cancer resection and liver metastases longer than 1 year [114]. In Thelen`s study the multivariate analysis revealed only resection margin as an independent prognostic factor for survival [116]. Shirabe concluded that synchronous hepatectomy should not be a contraindication for hepatic resection [111].

The results of liver resection in liver gastric metastases should not be discarded simply because of the lack of prospective, randomized data. For patients with hepatic disease amenable to surgical resection, treatment alternatives include systemic chemotherapy, locoregional ablative therapies with or without systemic treatment or surgical resection with or without systemic treatment. It is not unreasonable to consider liver resections in highly selected patients as part of multidisciplinary care for this malignancy.

For other non-colorectal gastrointestinal adenocarcinoma (esophageal, biliary, pancreatic cancers) the available evidence for hepatectomy is extremely limited, and this treatment strategy lacks utility. Most authors, despite having performed hepatectomies for these metastatic tumours, agree that it is associated with a poor prognosis. Occasionally, a patient with favourable tumour biology may be identified who will benefit from liver directed therapy.

2.3.5 Lung cancer

Liver resection for lung cancer metastases is rare and few numbers of cases are reported in the literature. The reported cases appear frequently associated with other kind of metastatic liver tumour in more large series. Lindlell et al., in the largest series, reported three cases but did not show the outcome [120]. Di Carlo reported a case of long-term survival [121].

When a patient has one or two liver nodules with more than one year of disease-free interval from the resection of primary tumour, hepatic resection can be a therapeutic option [122]. Liver involvement is managed surgically only under these exceptional circumstances.

2.3.6 Ovarian and testicular cancer

Epithelial ovarian cancer is a highly chemosensitive disease, and platinum-based therapies bring about significant diminution of tumour volume in most of the patients. Regrettably, the patients develop resistance to platinum chemotherapy after 24-36 months. Notwithstanding, many centres, despite stage III-IV advanced ovarian cancer, with a median survival of 3.5 years, propose very aggressive management with surgical debulking [123]. Multiple studies have shown an important survival benefit when primary cytoreductive surgery precedes the initiation of chemotherapy for advanced ovarian cancer. The benefits of cytoreductive surgery are also obvious in patients with recurrent disease. More than 70% of patients with advanced stage disease suffer recurrence and the benefits of second debulking depend on chemosensitivity, feasibility of surgery and tumour behaviour.

Liver is rarely the only site of metastatic ovarian cancer but also hepatectomy can be an important point of cytoreduction approach. Ovarian cancer can involve the liver through peritoneal lesions on the surface or with intraparenchymal metastases [124]. Survival is clearly improved for stage IV disease patients with complete and adequate debulking, even hepatectomy. Hepatic metastases should not preclude attempts at optimal secondary cytoreductive surgery. When cytoreductive resection is performed by pelvic and hepatobiliary surgeons, morbidity and mortality appear no different from that attributed to aggressive surgical debulking itself.

Metastasectomy is well established in the management of disseminated non-seminomatous germ cell testicular carcinoma that does not completely respond to chemotherapy. The key to success in the treatment of metastatic germ cell tumours is due to the multidisciplinary approach. Although after chemotherapy it can be difficult to differentiate active residual tumour from necrosis or fibrosis, the probability of achieving cure by surgical resection is high. For these reasons, lymphadenectomy and visceral resection are recommended if there is imaging evidence of residual disease [125]. In some cases complete excision requires multivisceral radical resections as a last attempt to cure patients who have exhausted all other therapeutic options. Complete surgical resection of all measurable disease is the gold standard and correlates with improvement in both relapse-free and overall survival after hepatectomy, with actuarial survival rates of 78% at 3 years in these tumours.

2.3.7 Renal cell carcinoma and urothelial cancer

Data on hepatic resection for renal cell cancer (RCC) and urothelial cancer (UC) liver metastases are limited to case reports. In metastatic RCC, the liver involvement is present in 20% of the patients and carries less than 10% of overall 1-year survival rate. Furthermore, only 5% of metastatic RCC patients have the liver as only involved organ. However, five-year survival of 33% has been reported following resection of lung, brain or lymph node metastases in association with chemotherapy in UC. Furthermore, metastasectomy has been used for palliation with good results [125]. However Alves et al. reported 46 liver resections for metastatic RCC patients with a 5-year survival of 13% [126].

These limited data determine inconsistent recommendations for hepatectomy in metastatic RCC and UC. In RCC, the use of sunitinib or sorafenib as neoadjuvant or post-hepatectmy therapy could improve the outcome.

3 Surgical treatment of resectable metastases

3.1 Resectability

Criteria for resectability are derived from the information obtained from the treatment of CLM, but may be applied to the liver metastases from others solid tumours. Pre-operative imaging techniques, patient selection, surgical techniques, postoperative care and new cytotoxic and biologic agents for preoperative and post-operative treatment have dramatically improved the resectability rate of liver metastases. The old criteria for resectability of CLM have accordingly changed: number of metastases is not a risk factor for survival whenever a R0 resection (complete resection with no microscopic residual tumour) is achieved [127]. In spite of some conflicting reports, evidence shows that size is not a resectability factor, but a factor related to the aggressiveness of the tumour. Likewise, the width of the surgical margin has no effect on survival providing that the margin is microscopically negative [128-130], though resection should attempt to get an optimum margin.

Few years ago extrahepatic disease was considered a contraindication to liver resection, but 5-year survival rates of 12% to 37% after surgery in selected patients, independent of the location of the extrahepatic disease (lung, colorectal recurrence, retroperitoneal or hepatic pedicle lymph nodes, peritoneal carcinomatosis, miscellaneous) have been reported [131-135]. Nevertheless, peritoneal disease contraindicates hepatic resection, but it can be considered in cases of stable or responsive disease to chemotherapy and when an R0 resection is achievable. These patients should be classified as borderline resectable [136]. Positive hilar lymph nodes are associated with a 5-year survival rate of 3%-12% after resection and are considered as a contraindication to liver resection of CLM, but there may be lengthy survival in some patients as long as the involved nodes are limited to the hepatoduodenal-retropancreatic area [137, 138]. A positive resection margin is the only traditional prognostic indicator of recurrence that precluded long-term survival [139].

In summary, just two criteria for resectability are significant: all disease should be removed with a negative margin and an adequate hepatic reserve should remain. That is to say, liver metastases are considered as resectable when they can be completely excised, two adjacent liver segments can be spared with an adequate vascular inflow and outflow and biliary drainage, and the volume of the future liver remnant (FLR) is sufficient (at least 20% of the total estimated volume for liver with normal parenchyma, 30%-60% for liver with chemotherapy, steatosis or hepatitis, 40%-70% for liver with cirrhosis) [136]. Clinically it is useful to estimate FLR to body weight ratio, which should be greater than 0.5. Contraindications of resection are non-resectable extrahepatic disease, a Child-Pugh score grade B and C and an inadequate performance status for surgery [25]. Notwithstanding, "resectability" of primary or metastatic liver cancer is not a clearly defined issue so that the experience of the individual surgeon plays an essential role.

3.2 Role of chemotherapy in CLM

Type of regimen and sequencing of chemotherapies when liver resection of CLM is possible are not clear, since the efficacy of peri-operative chemotherapy on survival for resectable liver metastases has not been justified. There is no evidence to support neoadjuvant chemotherapy in patients with resectable CLM [140]. Moreover, since around 7% of these

tumours will progress while on chemotherapy, a few patients may be compromised their chance of cure if this treatment is routinely used. Some authors suggest that, in the absence of high-risk features, treatment of CLM should begin with surgery and then consider adjuvant chemotherapy [141]. If high-risk features are present (perforated tumour or a considerable lymphatic burden, for instance), most surgeons prefer a course of systemic pre-operative chemotherapy before liver surgery.

The EORTC 40983 study evaluated peri-operative chemotherapy vs. surgery alone in resectable CLM and did not demonstrate a clear advantage of preoperative chemotherapy nor could determine either if neoadjuvant, adjuvant or peri-operative chemotherapy was superior. In this trial, the postoperative complication rate was statistically significantly increased in those patients who receive perioperative chemotherapy versus surgery alone. Supporters of peri-operative treatment point out that surgery is facilitated and that the treatment provides information on tumour biology [142]. Livers affected by chemotherapy are usually more rigid, more difficult to manage and tend to bleed more easily at surgery. Moreover, there are some questions to be answered about the management of "ghost lesions" after complete response that cannot be detected with IOUS.

When resection of liver metastases is considered appropriate, it is imperative to have a high quality abdominopelvic CT (or MRI) within a month of the date of surgery. Also a chest CT should be done at that time.

3.3 Technique

Intraoperative bleeding is the main cause of postoperative morbidity and mortality. On the other hand, blood transfusion is associated to a higher complication rate, longer hospital stay, increased risk of infectious complications, increased perioperative mortality and decreased long-term survival [143]. Thus, it is imperative to have a detailed knowledge of liver anatomy, a control of the vascular inflow and outflow, a low central venous pressure, intraoperative ultrasound and may be some other auxiliary devices (ultrasonic dissection, argon beam coagulation, etc.) to reduce blood loss during the resection.

In general, hepatic segmentectomy is preferable for localize lesions. Non-segmental resection may be technically more difficult and compromise the vascularity of adjacent residual liver. The Brisbane 2000 Terminology of Liver Anatomy and Resections is recommended to avoid confusion in the terms used when describing surgical techniques [144].

Regarding CLM, long-term survival is similar when comparing R1 (microscopically positive margins) with R0, despite a higher recurrence rate (5-year and 10-year overall survival rates are 61% and 43% in R0 vs. 57% and 37% in the R1) [145]. So it can be concluded that the inability to obtain a free surgical margin should not be a contraindication to surgery, as long as a complete macroscopic removal of all metastatic lesions is obtained.

After the first report of a laparoscopic liver resection in 1992 [146] this approach is more and more frequently performed but, although it shows advantages in the short term over open surgery, there are still no data to indicate the impact of this procedure on long-term outcome.

Liver surgery inflicts a mortality of less than 5% and a morbidity of around 30%, bearing in mind the wide variation in surgical aggressiveness. Postoperative hepatic failure, which depends on the volume and the function of the residual liver, can be a lethal complication.

Traditionally, a staged approach with initial resection of the primary disease followed by hepatic resection was recommended, but nowadays a simultaneous colon and liver resection is safe and efficient for CLM and LMNETs, since prognosis is not dependent on the time of resection [147-150]. Contraindications include the need for primary emergency surgery, a locally advanced colorectal tumour, or the need for major hepatectomy involving three or more segments. For other synchronous metastatic lesions simultaneous surgery can be safe but efficiency is much lower.

Resection of advanced synchronous liver metastases before resection of the primary disease is another option. The rationale is that it allows a better selection of patients who will benefit from surgery. More importantly, it focuses on the site and may reduce recurrence in the liver at distant sites, which might later occur after treating the primary tumour [151].

4 Surgical treatment of initially non-resectable metastases

When metastases are not firstly resectable because of an insufficient FLR, some techniques may be used. Strategies to increase the volume of the hepatic remnant include conversion chemotherapy, portal vein occlusion, staged liver resection and combination of these procedures. Also, ablative techniques may be considered alone or in conjunction with resection.

4.1 Conversion chemotherapy

Conversion chemotherapy is directed to downsize the tumour for looking at its resection. New chemotherapeutic regimens for CLM (adding oxaliplatin and/or irinotecan to 5-FU and folinic acid) have achieved response rates of around 50%, enabling 10-30% of initially unresectable patients to be operated [152]. Combined with biologic agents such as bevacizumab (a humanized monoclonal antibody that inhibits vascular endothelial growth factor A, thus impeding angiogenesis) or cetuximab (a monoclonal antibody that inhibits epidermal growth factor receptor in KRAS wild type colon cancer), response rates of up to 70% are achieved [139].

Hepatic arterial infusion (HAI) of chemotherapy may be added to systemic therapy, obtaining a higher concentration of drugs in the liver with less systemic toxicity but, although response rates are higher than systemic chemotherapy, survival does not change so far. Moreover, its complication rates are so high (57%) that it is discarded as a first option.

When preoperative chemotherapy is given, a new re-evaluation for resection should be done after 2 or 3 months and every 2 months thereafter. Systemic treatment should be stopped when lesions have been downsized to the point where hepatic resection is possible in order to reduce liver toxicity and to avoid a complete clinical response. A complete response on imaging studies does not mean cure since in over 80% of the cases of CLM there are viable cancer cells in the initial site of the metastasis [153]. Therefore, these ghost lesions have to be removed or ablated [154-156].

Systemic chemotherapy without the resection of bowel disease is associated with a shorter hospital stay and avoids surgery without a detrimental effect on survival for most patients. Medical therapy at the outset avoids the progression of disseminated disease. The development of an endoscopic transtumoral stent used to prevent occlusion is a useful nonsurgical treatment in this case [157].

Tumour progression while under chemotherapy is associated with a poor outcome, even after potentially curative hepatectomy. Hence, tumour control before surgery is crucial [152]. Peri-operative complications are more frequent with prolonged pre-operative chemotherapy [158]. Since this morbidity affects long-term survival [159], length of chemotherapy treatment must be taken into account.

4.2 Portal vein occlusion

Portal vein embolization (PVE), usually of the right portal branch, is directed to induce atrophy of the tumour-bearing lobe with subsequent hypertrophy in the contralateral lobe, by diverting the portal venous flow into the liver part that is expected to remain [160]. In general, two methods of portal vein occlusion can be employed: PVE or surgical portal vein ligation (PVL). Neither technique has clear advantage.

Portal occlusion increases the FLR between 10% to 46% within 2 to 8 weeks and enables an R0-resection in 70% to 100% of selected cases. It increases the chance of liver resection by 19%. However, some patients show tumour progression after PVE. When a hypertrophy greater than 5% is obtained the risk of a severe post-operative liver insufficiency is low [161]. The concomitant administration of chemotherapy does not seem to affect the hypertrophy.

Percutaneous PVE is usually well tolerated, with a complication rate below 5% [162]. The actuarial survival rate after surgery is 40% at 5 years, similar to that of patients resected without PVE [163].

4.3 Two-stage hepatectomy

When it is impossible to resect all liver metastases in a single procedure, two sequential liver resections may be done. The first surgery attempts to clear out of tumour the FLR, with non-anatomic resections and/or radiofrequency ablation or at most a single segment resection [164]. After a period of recovery of 4 to 6 weeks and the hypertrophy of the tumour-free lobe, tumour removal is completed by resection of the larger tumour mass in the contralateral liver lobe. The technique should be well designed in advance to try to achieve a complete removal, although around 30% of patients will not be rescued on the second hepatectomy because of progression of their disease in the meantime.

Furthermore, a PVE may be performed 2 to 4 weeks after the first stage and the second surgery can be done 4 or 6 weeks later, when a CT confirms an adequate hypertrophy of the non-embolized hemi-liver [165]. Alternatively, portal vein occlusion can be done during the first hepatectomy through the ligation and alcoholization of the right portal vein, which is the side more often embolized [166, 167].

Patients with a complete resection have a 5-year survival rate of 32%-51% [168,169]. Pre-operative chemotherapy may be given during the entire process.

4.4 Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)

This new technique consists in a two-staged extended right hepatectomy [170]. The first stage includes right PVL and in situ splitting (ISS) along the right side of the falciform ligament to induce rapid hypertrophy of the left lateral lobe: a median hypertrophy of 74% (above that achieved by PVL or PVE alone) after a median time interval of 9 days. This short time interval overrides the risk of tumour progression in the meantime.
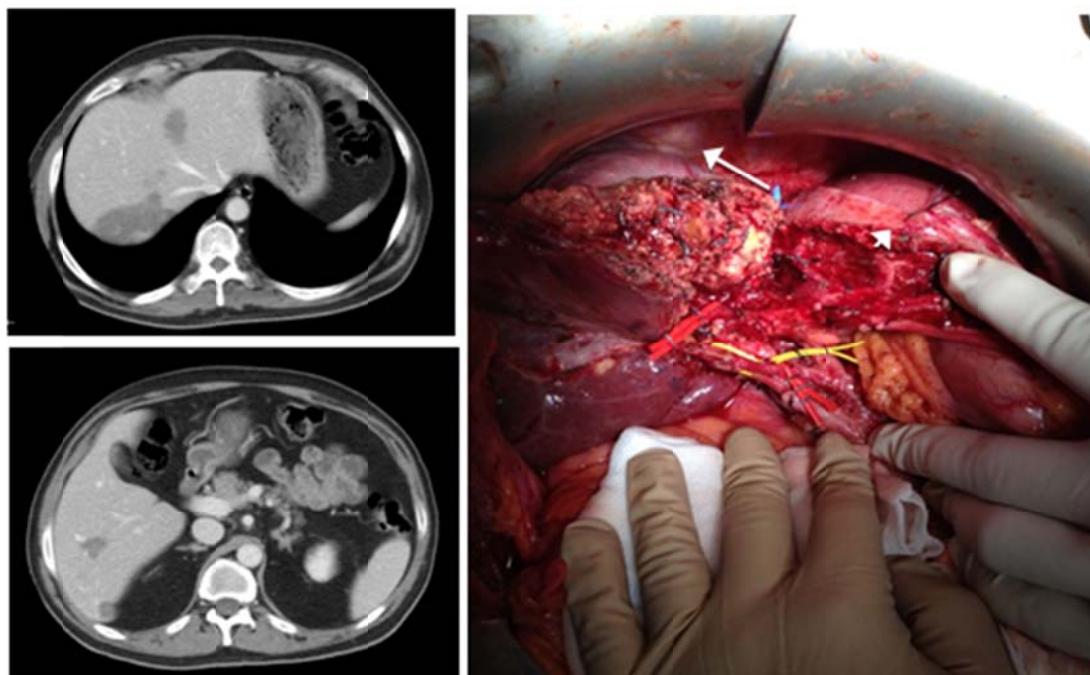

Figure 2. A 46 year-old male with 7 CLM and a FLR of 19.7%. After 9 cycles of chemotherapy, a FLR of 31.3% was achieved and an ALPPS was performed. CT showing CLM in Sg 4, 8 and 7 (above) and Sg 5-6 and 6 (below). Operative field: liver partition performed between Sg 4-8 (arrow) and Sg 2-3 (arrow head)

The technique is directed to patients with marginally resectable or primarily nonresectable primary and metastatic tumours. When an extended right hepatectomy is planned, the completeness of segment IV branch embolization may frequently be incomplete and progression of the segment IV tumour may impair a second stage.

Some drawbacks of ALPPS are an increased morbidity and mortality rates in the first reported series [171], a necrotic segment 4 in patients who could not be candidates for second stage because of insufficient hypertrophy [172] and little advantages over the previous techniques [173]. Advantages of ALPPS include an easier second procedure, a faster recovery for the patient, and the option of performing the colorectal resection simultaneously with the first step of the procedure, including the tumour cleaning of the FLR [174].

Additional research should be addressed about short- and long-term results, accelerated development of micrometastases on the future remnant liver, systemic stress responses affecting the second step of resection, and survival and progression patterns [175], to uncover the oncologic benefit of this new approach. With this purpose, a registry of these cases has been created [176] (Figure 2).

Laparoscopy has also been used in this technique, showing that it is feasible and may be worthwhile in experienced hands [177, 178].

4.5 Ablative techniques

Radiofrequency ablation (RFA) is obtained by the pass of alternating current across the lesion using a needle placed in the centre of the metastasis. The frictional heat causes coagulative necrosis and irreversible tissue injury. Vessels situated next to the ablated tissue interfere with the ablative techniques by the "heat sink effect". RFA treatment can achieve a 3-year survival rate of 25%. The combination of RFA and systemic chemotherapy has been shown to attain a 5-year survival rate of 30% [179, 180].

Morbidity and mortality are quite low (17% and 0.5%, respectively) [181].

Laser-induced thermotherapy (LITT) consists in the local administration of laser light to the tumour through fibers of quartz crystal. Morbidity and mortality are similar to RFA. Local tumour control at 6 months is reached in approximately 97% of the patients [182].

In microwave ablation (MWA), microwaves agitate water molecules in the tissue and produce frictional heat. Transmission is not limited by tissue desiccation and charring as in RFA, allowing higher intratumoral temperatures, a larger ablation zone, shorter treatment time, and more complete tumour killing. Five-year survival rates of 32% have been reported.

High-intensity focused ultrasound (HIFU) is administered with a lens-focused transducer that elevates the tissue temperature to 60°C. In addition, the mechanical effects of the high intensity ultrasound assist the destruction of the tumour cells. Adverse effects seem to be minor [183].

Cryotherapy uses liquid nitrogen or argon to cool tumour tissue down to -180°C. The formation of intracellular ice crystals leads to a mechanical destruction of the interstitium. An "ice-cracking" of the liver tissue is seen in 5 to 28% of the patients receiving the treatment. Five-year and 10-year survival rate of 44% and 19% are reported, respectively [184], but local recurrence and high complication rates (30%) have led to a diminishing use of this technique.

Despite these data, the precise role of ablative therapy is yet to be established. Patients with serious comorbidity and patients who decline surgery are good candidates, although there are significant risks. Patients with treatable extrahepatic disease or whose tumours have been downsized by chemotherapy but are not resectable may be also considered for ablative therapy.

4.6 Total vascular exclusion (TVE) procedures

Liver transplantation, reduced adult-sized liver for children, living related donor liver transplantation and split liver transplantation are techniques useful in liver resection. Tumours regarded as unresectable with standard techniques can be removed using in-situ, ante-situ and ex-situ or bench liver surgery. These techniques are based in the TVE of the liver and the perfusion of the organ by preservation hypothermic solution. They differ in the extent to which liver is mobilized from its vascular connections, hilum and caval vein. Usually, a veno-venous bypass is employed and a hypothermic preservation solution is instilled through the portal vein, which leads to a better tolerance to ischemia [185].

Tumours that involve vascular structures of the hilum, venous confluence or inferior vena cava (IVC) are the main indications. In the ante-situ procedure the division of the suprahepatic vena cava allows rotation of the liver around the coronary axis, providing optimal exposition of the venous confluents and the retrohepatic vena cava. In the ex-situ technique the liver is completely removed from the patient, allowing complex reconstructions of hepatic veins or portal structures, after which the liver is reimplanted. This procedure was described by Pichlmayr in 1988 and has been sparingly applied in selected patients [186, 187] due to its high morbidity and mortality.

Since the IVC can be resected and reconstructed with an autogenous vein graft or a prosthetic material, its involvement does not necessarily preclude resection. High morbidity and mortality rates (40% and 4.5%-25%, respectively) should be balanced by the possible benefits, particularly when the lack of alternative approaches is considered [188].

4.7 Re-resection: repeat hepatectomy

Recurrence may occur in up to 75% of CLM resected patients, 92% of them within the first 24 months after resection [189]. Although a half of these relapses are in the liver [190], only 5%-27% of the patients are considered for a repeated hepatectomy.

Each case of recurrent metastatic liver tumour needs a particular and specific evaluation. Although the prognostic variables provide rough indicators of prognosis, they should not be used as absolute contraindications to surgery.

Recurrence after repeat hepatectomy in CLM has been reported in 60%–80% of patients [191]. Some patients may be candidates for a third or even fourth hepatic resection. Between 9% and 30% of patients with a second hepatectomy have a third resection [19, 192-194] and around 4% of them have a fourth resection [195].

The safety of multiple repeated hepatic resections has been demonstrated, with a low mortality rate (0-2%) and a morbidity rate of 5%-30%. LiverMet Survey published the largest series (n = 251) of third hepatectomies for CLM showing a survival benefit of 29% at 5 years.

4.8 Associated extrahepatic disease (EHD)

Patients with liver metastasis and EHD have been considered as a subgroup with a very poor prognosis. EHD was traditionally considered a contraindication for liver resection, but survivals of 30% at 5 years, and higher than that achieved with chemotherapy only, have been obtained in some patients whose CLM and EHD have been resected [196]. Moreover, resection improves quality of life of these patients [197].

PET-CT can change the therapeutic approach in up to 25% of the patients, since infrequent sites of recurrences can be shown (bone, spleen, lymph nodes, etc.) On the other hand, around 5%-10% of the patients may benefit from the laparoscopic approach, which can detect peritoneal disease [198]. Treatment for patients with resectable CLM and EHD usually begin with 4 to 6 cycles of chemotherapy. If there is clinical response or stable disease, surgery is indicated. Progression contraindicates surgery.

When EHD is found during surgery (lymph nodes or peritoneal disease) the indication of resection becomes controversial [199].

There are few series of patients with CLM and EHD [200-204]. EHD was diagnosed preoperatively just in 40-65% of the cases. Morbidity and mortality were similar to that of resection of CLM (22%-31% and 0-4%, respectively). Up to 90% of the patients received postoperative chemotherapy. Five-year survival rate was 0-28%. Recurrence, usually in liver and lungs, appeared in 70%-95% of the patients, and was occasionally resected.

5 Conclusions

Aside from patients with colorectal and neuroendocrine tumours, liver resection may offer a significative survival advantage in selected patients. After a minimum disease-free interval of twelve months from the primary tumour, some patients may benefit from this aggressive treatment, mainly those with metastases from breast cancer, gastrointestinal stromal tumours and testicular, ovarian and renal cancer. Resection of metastases from others tumours exhibits shorter long-term survival, although the procedure should be considered on a case-by-case basis, particularly when confronted with the lack of alternative approaches.

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