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REVIEW

Role of surgical resection for non-colorectal non-neuroendocrine liver metastases

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Abstract

It is widely accepted that the indications for hepatectomy in colorectal cancer liver metastases and liver metastases of neuro-endocrine tumors result in relatively better prognoses, whereas, the indications and prognoses of hepatectomy for non-colorectal non-neuroendocrine liver metastases (NCNNLM) remain controversial owing to the limited number of cases and the heterogeneity of the primary diseases. There have been many publications on NCNNLM; however, its background heterogeneity makes it difficult to reach a specific conclusion. This heterogeneous disease group should be discussed in the order from its general to specific aspect. The present review paper describes the general prognosis and risk factors associated with NCNNLM while specifically focusing on the liver metastases of each primary disease. A multidisciplinary approach that takes into consideration appropriate timing for hepatectomy combined with chemotherapy may prolong survival and/or contribute to the improvement of the quality of life while giving respite from systemic chemotherapy.

Key words: Non-colorectal non-neuroendocrine liver metastasis; Metastatic liver tumor; Hepatectomy; Gastric cancer liver metastasis; Gastrointestinal stromal tumor liver metastasis; Breast cancer liver metastasis; Melanoma liver metastasis; Sarcoma liver metastasis; Renal cell carcinoma liver metastasis; Ovarian cancer liver metastasis

Core tip: Previous studies reported that the results of hepatectomy for non-colorectal, non-neuroendocrine liver metastasis (NCNNLM) showed an acceptable prognosis in the heterogeneous disease group. However, considering the indication of hepatectomy for NCNNLM, it is important to define the features of each primary disease. The present review paper describes the general prognosis and risk factors associated with NCNNLM, specifically focuses on liver metastasis associated with each primary disease. A multidisciplinary

approach that takes appropriate timing for hepatectomy combined with chemotherapy into consideration may prolong survival and/or contribute to the improvement of the quality of life, while taking time off from systemic chemotherapy.

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INTRODUCTION

Metastatic disease from solid organ tumors occurs frequently in the liver. Presently, surgical resection has been widely accepted as a treatment for colorectal cancer liver metastases[1,2] and liver metastases of neuro-endocrine tumors[3,4], providing a relatively better prognosis, whereas, the indications and prognosis of hepatectomy for non-colorectal non-neuroendocrine liver metastases (NCNNLM) remain controversial owing to the rarity of the disease. The biological behavior of NCNNLM varies depending on its primary origin. Discussion of this heterogeneous disease group should be performed in the order from its general to specific aspects. To date, no prospective randomized study has been conducted in this limited field; therefore, in this report we provide a general review of large cohort retrospective studies on hepatectomy for NCNNLM and a more specific review on hepatectomy for liver metastases from different primaries.

LITERATURE AND RESEARCH

In this report, we reviewed the literature reporting NCNNLM in a large number of patients and their specific primaries. More precisely, we reviewed articles in the English literature that included ⩾ 100 cases with NCNNLM and relatively large case series for the specific primary (for liver metastases from gastric cancer, breast cancer, and melanoma, reports that included ⩾ 40 cases were reviewed because of the limited availability of cases in many studies). Using the results reported in the selected literature, the survival outcomes and statistically significant risk factors that impacted survival by multivariate analysis (univariate analysis for some report) were evaluated.

Prognosis and risk factors after hepatectomy for NCNNLM

Along with increased evidence of prolonged survival by hepatectomy in patients with colorectal and neuroendocrine liver metastases, Schwartz *et al*[5] initially categorized NCNNLM and reviewed the literatures in 1995, followed by the analysis of prognosis in a large cohort study by Harrison *et al*[6] in 1997. Many validation studies were performed in other patient cohorts that are summarized in Table 1[7-16]. In the present report, we reviewed the 10 largest studies, each with ⩾ 100 patients who underwent hepatectomy for NCNNLM. In this cohort, the 3- and 5-year overall survival rates were reported as 34%-57% and 19%-42%, respectively, with median survival times of 23-49 mo. The 3- and 5-year disease-free survival rates were 21%-37% and 18%-29%, respectively, with median disease-free survival times of 10-21 mo. The postoperative mortality and morbidity rates were reported 0%-5% and 18%-33%, respectively. In these cohort studies, the reported negative risk factors for survival were the margin status in six studies[8-11,15,16]; primary tumor type in four[8,10,11,15]; shorter disease-free interval between primary tumor resection and hepatectomy[8,10,15] and extrahepatic disease[10,12,16] in three; postoperative complications[14,16], larger hepatic metastasis in diameter[12,13], and squamous cell histology[10,15] in two; and age[10], major hepatectomy[10], minor hepatectomy[15], synchronous metastasis[11], lymphovascular invasion[13], stromal tumor histology[15] and > 3 liver metastases[16] in one (Table 1). Negative risk factors for recurrence were extrahepatic disease[12,16] in two studies; and primary tumor[8], disease-free interval[8], larger hepatic metastasis in diameter[12], blood transfusion[14], preoperative chemotherapy[14], > 3 liver metastases[16], and residual tumor[16] in one. Patients with liver metastases from breast cancer showed significantly better survival in three studies[10,11,15], whereas those with liver metastases from genitourinary tumor liver showed better survival in one[11], and patients with liver metastases from melanoma showed poorer survival compared to other primaries in two studies[10,15] (Table 2).

As previously mentioned, the type of primary origin was one of the greatest predictors of survival in patients with this heterogeneous disease. Among the 10 largest studies, the most dominant primary origin was the breast[7,10,13,15] and genitourinary[8,11,12,16] in four studies and gastrointestinal tract in two[9,14]. Elias *et al*[7] and Yedibela *et al*[9] commented that the resection of liver metastases from gastrointestinal adenocarcinoma correlated with a poor prognosis; however, a more recent report by Takemura *et al*[14] showed acceptable prognosis after resection of liver metastases from gastrointestinal carcinoma in their largest cohort with a median survival time of 33.5 mo after hepatectomy. As Yedibela *et al*[9] and Groeschl *et al*[13] reported that in the more recent years, patients undergoing hepatectomy for NCNNLM appeared to have longer survival compared to previous years, advances in chemotherapy regimens might contribute to prolong survival after the resection of NCNNLM. Adam *et al*[10] developed a risk model based on their results of multivariate prognostic factor analysis, which was validated by Lendoire *et al*[11]. Their risk model can efficiently stratify the patients into groups; however, the prognosis of each group differed between the two studies depending on the heterogeneous backgrounds of the patient. To facilitate discussion, the prognosis of each primary disease after hepatectomy for NCNNLM has been discussed separately in following section.

Table 1 Summary of studies each of which included ⩾ 100 patients who underwent hepatectomy for non-colorectal non-neuroendocrine liver metastases (overall survival)

Ref.	Year	Period	No. of patients	Primary tumor (GI/breast/GU/ melanoma/sarcoma/others)	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Elias *et al*[7]	1998	1984-1996	120[1]	(22/35/31/10/13/9)	NR	NR	36[2]	NR
Yedibela *et al*[9]	2005	1978-2001	150[1]	(50/24/11/5/15/45)	23[2]	NR	26[2]	Margin status (R1,2)
Weitz *et al*[8]	2005	1981-2002	141	(12/29/50/17/0/33)	42	57	NR	Primary tumor type, disease-free interval ⩽ 24 mo, margin status (R1,2)
Adam *et al*[10]	2006	1983-2004	1452	(314/460/332/148/0/198)	35	49	36	Age, primary tumor (ocular melanoma, non-breast), squamous tumor, disease-free interval, extrahepatic disease, major hepatectomy, margin status (R1,2)
Lendoire *et al*[11]	2007	1989-2006	106	(7/19/40/6/23/11)	27	34	19	Primary tumor (non-breast, non-GU), synchronous metastasis, margin status (R1,2)
O'Rourke *et al*[12]	2008	1986-2006	102	(27/11/31/20/3/10)	42	56	39	Diameter of liver metastasis > 5 cm, extrahepatic nodal disease
Groeschl *et al*[13]	2012	1990-2009	420	(13/15/92/31/98/71)	49	50	31	Diameter of liver metastasis ⩾ 5 cm, lymphovascular invasion
Takemura *et al*[14]	2013	1993-2009	145	(91/30/12/1/8/3)	42	55	41	Postoperative complication
Hoffmann *et al*[15]	2015	2001-2012	150	(30/42/33/15/9/21)	46	NR	42	Primary tumor (melanoma, non-breast), interval < 24 mo, squamous tumor, non-stromal tumor, minor hepatectomy, margin (R2)
Schiergens *et al*[16]	2016	2003-2013	167	(43/16/61/8/25/14)	35	49	NR	> 3 liver metastases, extrahepatic disease, residual tumor (R1,2), major complications

[1]Patients with neuroendocrine tumors were excluded; [2]Results including neuroendocrine tumors. GI: Gastrointesti; GU: Genitourinary; MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 2 Summary of studies each of which included ⩾ 100 patients who underwent hepatectomy for non-colorectal non-neuroendocrine liver metastases (disease-free survival)

Ref.	Year	No. of patients	MDFST (mo)	3-ydfsr (%)	5-ydfsr (%)	Factors associated with worse disease-free survival
Elias *et al*[7]	1998	120[1]	NR	NR	28[2]	NR
Yedibela *et al*[9]	2005	150[1]	NR	NR	NR	NR
Weitz *et al*[8]	2005	141	17	30	NR	Primary tumor, diseas-free interval ⩽ 24 mo
Adam *et al*[10]	2006	1452	13	27	21	NR
Lendoire *et al*[11]	2007	106	NR	NR	NR	NR
O'Rourke *et al*[12]	2008	102	18	37	27	Diameter of liver metastasis > 5 cm, extrahepatic nodal disease
Groeschl *et al*[13]	2012	420	NR	NR	NR	NR
Takemura *et al*[14]	2013	145	10	21	18	Blood transfusuion, preoperative chemotherapy
Hoffmann *et al*[15]	2015	150	21	36	29	NR
Schiergens *et al*[16]	2016	167	15	NR	NR	> 3 liver metastases, extrahepatic disease, residual tumor (R1,2)

[1]Patients with neuroendocrine tumors were excluded; [2]Results including neuroendocrine tumors. MDFST: Median disease-free survival time; ydfsr: Year disease-free survival ratio; NR: Not reported.

LIVER METASTASES FROM GASTROINTESTINAL PRIMARY TUMORS

Gastric cancer liver metastases

In the present report, we reviewed the largest 8 studies, each with ⩾ 40 patients who underwent hepatectomy for liver metastases from gastric cancer. In this series, the 3- and 5-year overall survival rates were reported as 14%-51% and 9%-42%, respectively, with median survival times of 12-41 mo (Table 3)[10,17-23]. Among these studies, the negative risk factors for survival were multiple liver metastases in three studies[18,20,23]; larger hepatic metastasis in diameter[19,21] and serosal invasion of primary gastric cancer[19,21] in two; and synchronous hepatic metastases[17], > 3 liver metastases[21] and > 2 positive regional lymph node metastases of primary gastric cancer[23] in one (Table 3). The results of hepatectomy for liver metastasis from gastric cancer are influenced by the statuses of both the primary cancer and liver metastasis. The recent meta-analysis of gastric cancer liver metastases revealed that the surgical resection of liver metastases from gastric cancer was associated with a significantly improved survival and among the patients who underwent surgical resection, patients with solitary hepatic metastasis demonstrated a significantly prolonged survival compared to patients with

Table 3 Summary of studies each of which included ⩾ 40 patients who underwent hepatectomy for liver metastasis from gastric cancer

Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Ambiru *et al*[17]	2001	1975-1999	40	12	NR	18	Synchronous metastasis
Adam *et al*[10]1	2006	1983-2004	64	15	NR	27	NR
Cheon *et al*[18]	2008	1995-2005	41	18	32	21	Multiple liver metastases
Takemura *et al*[19]	2012	1993-2011	64	34	50	37	Serosal invasion of primary gastric cancer, maximum hepatic metastasis diameter > 5 cm
Aizawa *et al*[20]	2014	1997-2010	53	27	NR	18	Multiple liver metastases
Kinoshita *et al*[21]	2014	1990-2010	256	31	42	31	Serosal invasion of primary gastric cancer, > 3 liver metastases, maximum hepatic metastasis diameter > 5 cm
Tiberio *et al*[22]	2015	1997-2011	53	13	14	9	NR[2]
Oki *et al*[23]	2015	2000-2010	69	41	51	42	Multiple liver metastases, > 2 positive regional lymph node metastases of primary gastric cancer

[1]As a part of the report of on-colorectal non-neuroendocrine liver metastases; [2]Only risk factors including palliative patients were reported. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 4 Summary of studies with relatively large cohort of patients who underwent hepatectomy for liver metastasis from gastrointestinal stromal tumors

Ref.	Year	Period	No. of patients underwent hepatectomy	MST (mo)	3-ysr (%)	5-ysr (%)	3-yPFS (%)	No. of patients with TKI	Factors associated with worse overall survival
DeMatteo *et al*[26]	2001	1982-2000	34[1]	39[1]	50[1]	30[1]	45[1]	NR	Interval from primary tumor diagnosis ⩽ 24 mo[2]
Nunobe *et al*[27]	2005	1984-2003	18	36	64	34	NR	3 (17%)	NR
Xia *et al*[28]	2010	2005	19	33 (mean)	90	NR	NR	19 (100%)	Non-surgical therapy[2]
Turley *et al*[29]	2012	1995-2010	39	Not reached at 5 yr	68	NR	NR	27 (73%)[3]	Non-TKI therapy, extrahepatic disease
Bauer *et al*[30]	2014	Until 2011	104	96	NR	NR	NR	> 84%	Male[4], R2 resection[4], progression disease to TKI at the time of surgery[4], extrahepatic disease[4]
Du *et al*[31]	2014	NR	19	Not reached	NR	NR	88 (2-yr)	19 (100%)	Non-surgical therapy[2]
Seesing *et al*[32]	2016	1999-2014	48	90	80	76	67	42 (88%)	Margin status (R1,2)

[1]Including gastrointestinal sarcoma; [2]Copmarison to the non-operation group; [3]Excluding two patients lost to follow-up; [4]Results including resections of extrahepatic metastasis. GIST: Gastrointestinal stromal tumor; MST: Median survival time; ysr: Year survival rate; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; NR: Not reported.

multiple hepatic metastases[24]. Compared to colorectal liver metastasis, reports on aggressive repeat hepatectomy have been highly limited[25], which might be owing to the frequent occurrence of extrahepatic recurrence such as peritoneal seeding and lymph node recurrence. However, advancements in effective chemotherapy regimens can expand not only the prognosis but also the surgical indications for hepatectomy in patients with liver metastasis from gastric cancer and colorectal live metastases alike.

Gastrointestinal stromal tumors liver metastases

The 7 largest studies on the hepatectomy for liver metastases from gastrointestinal stromal tumors (GIST) reported 50%-90% and 30%-76% overall 3- and 5-year survival rates, respectively, with median survival times of 33-96 mo (Table 4)[26-32]. Non-surgical therapy[28,31], positive resection margin[30,32], and extrahepatic disease[29,30] in two studies each and a disease free interval ⩽ 24 mo[26], absence of tyrosine kinase inhibitor (TKI) therapy[29], male patients[30] and progression disease to TKI therapy at the time of surgery[30] were the factors associated with worse survival (Table 4). Different from other NCNNLMs, the emergence of TKI dramatically changed the treatment and prognoses of patients with advanced GIST. The role of surgical resection in the treatment of metastatic GIST had remained unclear in the initial era of treatment with TKI[33]; however, recent reports showed evidence that surgical resection combined with TKI offered better prognosis than TKI monotherapy[29,31,32]. As Bauer *et al*[30] reported progression disease to TKI therapy at the time of surgery, an urgent issue to debate is the appropriate duration of preoperative therapy to minimize the risk of acquiring secondary mutations responsible for TKI resistance[26,29].

Other gastro-intestinal primary tumor liver metastases

Pertaining to reports of liver resection for other gastrointestinal primary liver metastases that rarely indicated hepatectomy, esophagus and pancreas cancer liver metastasis showed dismal prognosis with a median overall survival time of 7-20 mo[10,16,34,35]. In the mean-

Table 5 Summary of studies with relatively large cohort of patients who underwent hepatectomy for liver metastases from gastrointestinal primaries other than gastric cancer and gastrointestinal stromal tumors

Disease	Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Peri-ampullary	De Jong *et al*[34]	2010	1993-2009	40	17 [23 (intestinal), 13 (pancreaticobiliary)]	18	NR	Intestinal type (ampullary or duodenal) tumors
Ampullary	Adam *et al*[10]1	2006	1983-2004	15	38	NR	46	NR
Small bowel	Adam *et al*[10]1	2006	1983-2004	28	58	NR	49	NR
Pancreas	Adam *et al*[10]1	2006	1983-2004	40	20	NR	25	NR
	Schiergens *et al*[16]1	2016	2003-2013	19	7	17	NR	NR
Esophagous	Adam *et al*[10]1	2006	1983-2004	20	16	32	NR	NR
	Ichida *et al*[35]	2013	2003-2005	5	13	NR	NR	NR

[1]As a part of the report of on-colorectal non-neuroendocrine liver metastases. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 6 Summary of studies with ⩾ 40 patients who underwent hepatectomy for liver metastasis from breast cancer

Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	MDFS (mo)	Factors associated with worse overall survival
Pocard *et al*[36]	2000	1988-1997	52	42	49	NR	NR	Disease free interval ⩽ 48 mo (univariate)
Elias *et al*[37]	2003	1986-2000	54	34	50	34	NR	Hormone receptor-negative
Adam *et al*[38]	2006	1984-2004	85	32	NR	37	20	Poor response to preoperative chemotherapy, R2, no repeat hepatectomy
Adam *et al*[10]1	2006	1983-2004	454	45	NR	41	NR	NR
Hoffman *et al*[39]	2010	1999-2008	41	58	68	48	34	Positive resection margin, disease-free interval < 24 mo
Abbott *et al*[40]	2012	1997-2010	86	57	NR	44	14	ER-negative, disease progression before hepatectomy
Groeschl *et al*[13]1	2012	1990-2009	115	52	52	27	22	NR
Mariani *et al*[41]	2013	1988-2007	51	91	NR	NR	NR	Non-hepatectomy[3], bone metastasis[4]
Hoffmann *et al*[15]1	2015	2001-2012	42	63	NR	53	NR	NR
Sadot *et al*[42]	2016	1991-2014	69[2]	50[2]	NR	38[2]	29	Lymph node metastasis in the primary tumor, absence of trastuzumab therapy, multiple liver metastases

[1]As a part of the report of on-colorectal non-neuroendocrine liver metastases; [2]Including 18 patients who underwent percutaneous ablation therapy; [3]Comparison to the non-operation group; [4]Comparison including patients without hepatectomy. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

while, intestinal type primary tumors such as duodenal, ampullary and small intestinal cancer showed relatively better prognosis with median survival times of 23-58 mo[10,34] (Table 5).

LIVER METASTASES FROM BREAST CANCER

The largest 10 studies, each with ⩾ 40 patients who underwent hepatectomy for liver metastases from breast cancer were reviewed. In this series, the 3- and 5-year overall survivals rates were 49%-68% and 27%-53%, respectively, with median survival times of 41-115 mo (Table 6)[10,13,15,36-42]. The negative prognostic predictive factors were short disease-free interval[36,39], negative expression of hormone receptors[37,40], poor response to systemic chemotherapy before surgery[38,40], and positive hepatic resection margin[38,39] in two studies; and the absence of repeat hepatectomy[38], non-hepatectomy[41], bone metastasis[41], lymph node metastasis in the primary tumor[42], absence of trastuzumab therapy[42], and multiple liver metastases[42] in one (Table 6). Some prognostic factors of liver metastases from breast cancer are unique and different from other NCNNLMs, which could indicate that the presence of hormone receptors and HER2 overexpression requires the use of chemotherapy and/or hormone therapy and influences patient survival. Neuman *et al*[43] suggested that the impact of local control for liver metastases from breast cancer was greatest in the presence of effective targeted therapy. Similar to other NCNNLMs, surgical resection before progression of disease even with chemotherapy might result in better outcomes of selected patients with liver metastases from breast cancer[40]. As Sadot *et al*[42] advocated in their study, hepatic resection for liver metastases from breast cancer might not confer a survival advantages; however, might allow time off from systemic chemotherapy.

LIVER METASTASES FROM MELANOMA

The largest four studies, each with ⩾ 40 patients who underwent liver resection for liver metastases from melanoma, reported an overall 5-year survival rate of approximately 7%-20% with a median survival time of 14-28 mo (Table 7)[10,44-46]. Short disease-free interval from the diagnosis of primary tumor[45], positive resection

Table 7 Summary of studies with ≥ 40 patients who underwent hepatectomy for liver metastasis from melanoma

Ref.	Year	Period	No. of patients	Ocular/ cutaneous	MST (mo) (ocular/ cutaneous)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Adam *et al*[10]1	2006	1983-2004	148	104/44	19/27	NR	21 (ocular)/22 (cutaneous)	NR
Pawlik *et al*[44]	2006	1988-2004	40	16/24	28 [29 (ocular)/24 (cutaneous)]	62 (ocular)/48 (cutaneous) (2-yr)	11 (21 (ocular)/0 (cutaneous))	Cutaneous melanoma, no preoperative chemotherapy (in cutaneous melanoma) (univariable)
Mariani *et al*[45]	2009	1991-2007	255 (R2 = 157)	255/0	14 (27 mo after R0 resection)	NR	7	Interval from primary tumor diagnosis ≤ 24 mo, R1 and R2, number of the metastases > 4, miliary disease
Mariani *et al*[46]	2016	2000-2013	70 (inclding 13 concomitant with RFA)	70/0	27 (hepatectomy), 28 (+RFA)	NR	NR	NR

[1]As a part of the report of on-colorectal non-neuroendocrine liver metastases. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 8 Summary of studies with relatively large cohort of patients who underwent hepatectomy for liver metastasis from sarcoma

Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Lang *et al*[48]	2000	1982-1996	26 (including 9 second, 2 third resection)	32 (R0 first resection), 21 (R1,2 resection)	NR	13	NR
DeMatteo *et al*[26]1	2001	1982-2000	56[1]	39[1]	50[1]	30[1]	Time to liver metastasis from the primary tumor diagnosis ≤ 24 mo
Pawlik *et al*[49]	2006	1996-2005	53 (35Hx, 18RF + Hx, and 13RF), (including 36 GISTs)	47[2]	65[2]	27[2]	Non-GIST
Marudanayagam *et al*[50]	2011	1997-2009	36[1] (including 5 GISTs)	24	48	32	Primaly leiomyosarcoma
Groeschl *et al*[13]3	2012	1990-2009	98	72	60	32	NR
Zhang *et al*[51]	2015	2000-2009	27	NR	NR	46	Interval from primary tumor diagnosis ≤ 24 mo, extrahepatic disease, positive margins

[1]Including some patients with GIST before 1993, GISTs were considered as leiomyosarcomas; [2]Including results of RF and patients with GIST; [3]As a part of the report of on-colorectal non-neuroendocrine liver metastases. GIST: Gastrointestinal stromal tumor; MST: Median survival time; ysr: Year survival rate; NR: Not reported; Hx: Hepatectomy; RF: Radiofrequency ablation.

margin[45], > 4 liver metastases[45], miliary disease of the primary melanoma[45], cutaneous melanoma[46], and no preoperative chemotherapy were the risk factors predicting poor patients survival (Table 7). The metastatic pathway of ocular and cutaneous melanomas is different. Ocular melanoma often spreads hematogenously to the liver because there are no lymphatics in the uveal tract. In contrast, cutaneous melanomas potentially spread to the lung, lymph node and soft tissue, and infrequently to the liver[47]. Liver metastases from ocular melanoma often recur within the liver, whereas cutaneous melanoma is more likely to develop extrahepatic recurrence[44]. Surgical resection should be performed concomitantly with system in chemotherapy as part of a multidisciplinary approach because recurrent disease frequently develops after hepatectomy.

LIVER METASTASES FROM SARCOMA

The six largest studies on the resection of liver metastases from sarcoma reported 50%-65% and 13%-46% overall 3- and 5-year survival rates, respectively, with median survival times of 24-72 mo (Table 8)[13,26,48-51]. Negative risk factors for overall survival in this cohort were a time of < 24 mo from the diagnosis of primary tumor to the time of liver metastasis[26,51], non-GIST[49], leiomyosarcoma[50], extrahepatic disease[51], and positive resection margins[51] (Table 8). These studies included some GIST patients particularly in the early study periods because GIST had been considered as leiomyosarcoma before around 1993. Repeat hepatic resection was reported in four studies. Lang *et al*[48] reported 9 second and 2 third cases of hepatectomy for intrahepatic recurrent sarcoma. Less sensitivity to chemotherapy might prompt the surgeon to conduct a repeat hepatectomy with R0 resection, resulting in a favorable outcome[48].

LIVER METASTASES FROM GENITOURINARY TUMORS

Genitourinary tumors mainly comprise renal cell carcinoma, gynecological carcinoma most commonly with ovarian cancer, and testicular cancer. In the present report, we have reviewed 6 studies pertaining to liver metastases from the renal cell carcinoma which reported

Table 9 Summary of studies with relatively large cohort of the patients who underwent hepatectomy for liver metastasis from genitourinary primary tumor

Disease	Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Renal cell carcinoma	Adam *et al*[10]1	2006	1983-2004	85	36	NR	38	NR
	Thelen *et al*[52]	2007	1988-2006	31	48	54	39	Resection margin (R1,2)
	Staehler *et al*[53]	2010	1995-2006	68	142	NR	62	High-grade primary renal cell carcinoma, performance status ⩾ 1, lymph node status
	Ruys *et al*[54]	2011	1990-2008	29	33	47	43	Synchronous metastases, R1,2 resection margin (univariate)
	Hatzaras *et al*[55]	2012	1994-2011	43	Not reached	62	NR	Disease-free interval ⩽ 12 mo, exrahepatic disease (univariate)
	Schiergens *et al*[16]1	2016	2003-2013	28	50	68	NR	NR
Gyneclogic primary	Kamel *et al*[56]	2011	1990-2010	52	53	57	41	NR
Ovarian cancer	Merideth *et al*[57]	2003	1976-1999	26[2]	26	NR	NR	Interval from the primary diagnosis < 12 mo, residual disease > 1 cm (univariate)
	Adam *et al*[10]1	2006	1983-2004	65	98	NR	50	NR
	Lim *et al*[58]	2009	2001-2008	14[2]	Not reached	NR	51	Hematogeneous liver metastasis < hepatic parenchymal metastasis from peritoneal seeding[5]
	Neumann *et al*[59]	2012	1991-2007	41	42(R0 resection)	NR	NR	R1,2 resection, pre-operative ascites, bilobular liver metastasis
	Niu *et al*[60]	2012	2000-2011	60	39	NR	30	R1,2 resection
	Kolev *et al*[61]	2014	1988-2012	27[3]	56	NR	NR	Interval from the primary surgery ⩽ 24 mo, residual disease ⩾ 1 cm
	Bacalbasa *et al*[62]	2015	2002-2014	31[2,4]	16 (metastasis from seeding), 13 (hematogeneous)	NR	NR	No significant risk factor
	Schiergens *et al*[16]1	2016	2003-2013	24	33	43	NR	NR
Testicular cancer	Hahn *et al*[63]	1999	1974-1996	57	NR	97 (2-yr)	NR	NR
	Adam *et al*[10]1	2006	1983-2004	78	82	NR	51	NR

[1]As a part of the report of on-colorectal non-neuroendocrine liver metastases; [2]As a part of debulking surgery; [3]Hepatectomy as secondary cytoreduction; [4]Including 2nd (n = 15), 3rd (3) and 4th (2) cytoreduction operations; [5]Only risk factors that included patients undergoing palliative treatment were reported. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

overall 3- and 5-year survival rate of 54%-68% and 38%-62%, respectively, with median survival times of 33-142 mo (Table 9)[10,16,52-55]. The negative prognostic risk factors were the resection margin[52,54], high-grade tumor[53], poor performance status[53], lymph node metastasis[53], synchronous metastasis[54], short disease-free interval[55], and extra hepatic disease[55] (Table 9). Staehler *et al*[53] is the first to advocate a favorable prognosis for hepatectomy in patients who underwent resection of liver metastases from renal cell carcinoma over the prognosis of patients who refused to undergo hepatectomy for metastatic renal cell carcinoma, albeit the requirement for further systemic treatment.

The nine largest studies pertaining to gynecological primary cancers, particularly with ovarian cancer, reported 5-year overall survival rates of 30%-51% with median survival times of 26-98 mo (Table 9)[10,16,56-62]. Factors associated with worse survival were shorter interval from the diagnosis of primary disease to metastasis[56,61], residual tumor measuring > 1 cm[56,61], hematogenous liver metastasis[57], positive resection margins[59,60], pre-operative ascites[59], and bi-lobular hepatic metastasis[59] (Table 9). Owing to the unique features of ovarian cancer, hepatectomy was regarded as a part of cytoreductive surgery and concomitant chemotherapy, which has been accepted as the standard treatment for advanced ovarian cancer. In contrast to other NCNNLMs, the resection of liver metastases from the peritoneal seeding showed better prognosis than resection of hematogenous liver metastases[57].

Chemotherapy is highly effective in the treatment of testicular carcinoma; however, one-third of the patients either did not achieve complete responces or experienced relapses[63]. The limited studies involving treatment with sensitive chemotherapy and subsequent hepatectomy for testicular carcinoma have sufficiently demonstrated a favorable prognosis in patients who underwent this treatment regimen[63].

CONCLUSION

The clinical evidence accumulated with regards to NCNNLM has indicated the possibility of a chemotherapy-free period and a few studies have demonstrated a curing potential; however, almost all studies reviewed in the present report were conducted retrospectively in selected patients who underwent hepatic resection, which makes determining the absolute indications for hepatectomy in patients with NCNNLM challenging. Indications of hepatectomy for NCNNLM change according to the development of chemotherapy regimens. Strong and highly effective chemotherapy regimens might either expand the indications for hepatectomy or replace hepatectomy in this field. A multidisciplinary approach is

required for the treatment of patients with diseases that are otherwise difficult to treat.

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