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

Nobuyuki Takemura, Akio Saiura

Nobuyuki Takemura, Department of Gastroenterological Surgery, JR Tokyo General Hospital, Tokyo 151-8528, Japan
Nobuyuki Takemura, Akio Saiura, Department of Gastroenterological Surgery, Cancer Institute Ariake Hospital, Japanese Foundation for Cancer Research, Tokyo 151-8528, Japan

Author contributions: Takemura N analyzed the literatures and wrote the manuscript; Saiura A reviewed and edited the manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare in relation to the contents of this review.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Nobuyuki Takemura, MD, Department of Gastroenterological Surgery, JR Tokyo General Hospital, 2-1-3, Yoyogi, Shibuya-ku, Tokyo 151-8528, Japan. takemuranobu-thy@umin.ac.jp
Telephone: +81-3-33202200
Fax: +81-3-33707477

Received: August 30, 2016
Peer-review started: September 1, 2016
First decision: September 29, 2016
Revised: October 29, 2016
Accepted: December 7, 2016
Article in press: December 9, 2016
Published online: February 18, 2017

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

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Takemura N, Saiura A. Role of surgical resection for non-colorectal non-neuroendocrine liver metastases. World J Hepatol 2017; 9(5): 242-251 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/242.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.242

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[2,3] and liver metastases of neuro-endocrine tumors[4,5], 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[6] initially categorized NCNNLM and reviewed the literatures in 1995, followed by the analysis of prognosis in a large cohort study by Harrison et al[7] 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[8,10,11,15], and extrahepatic disease[10,12,16] in three; postoperative complications[4,12,16], larger hepatic metastasis in diameter[12,13], and squamous cell histology[10,15] in two; and age[16], 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 extrhepatic 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[12], 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[8] 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[15] 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[11] 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.
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)\(^{19,20,23}\). 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\(^{22}\) and > 2 positive regional lymph node metastases of primary gastric cancer\(^{22}\) 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 1  Summary of studies each of which included ≥ 100 patients who underwent hepatectomy for non-colorectal non-neuroendocrine liver metastases (overall survival)

| Ref.          | Year | No. of patients | MST (mo) | Factors associated with worse overall survival |
|---------------|------|-----------------|----------|-----------------------------------------------|
| Elias et al\(^{7}\) | 1998 | 120\(^1\)       | NR       | NR                                            |
| Yedibela et al\(^{4}\) | 2005 | 150\(^1\)       | 23\(^2\)  | 26\(^2\)                                      |
| Schiergens et al\(^{14}\) | 2016 | 167             | 35       | 49                                            |

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) | Factors associated with worse disease-free survival |
|---------------|------|-----------------|------------|----------------------------------------------------|
| Elias et al\(^{7}\) | 1998 | 120\(^1\)       | NR         | NR                                                 |
| Yedibela et al\(^{4}\) | 2005 | 150\(^1\)       | 30         | NR                                                 |
| Schiergens et al\(^{14}\) | 2016 | 167             | > 3 liver metastases, extrahepatic disease, residual tumor (R1,2), major complications |

1Patients with neuroendocrine tumors were excluded; 2Results including neuroendocrine tumors. GI: Gastrointestinal; GU: Genitourinary; MST: Median disease-free survival time; ydfsr: Year disease-free survival rate; NR: Not reported.
multiple hepatic metastases\textsuperscript{24}. Compared to colorectal liver metastasis, reports on aggressive repeat hepatectomy have been highly limited\textsuperscript{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 liver 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)\textsuperscript{26-32}. Non-surgical therapy\textsuperscript{28,31}, positive resection margin\textsuperscript{30,32}, and extrahepatic disease\textsuperscript{30,33} in two studies each and a disease free interval \(\leq 24\) mo\textsuperscript{28} of absence of tyrosine kinase inhibitor (TKI) therapy\textsuperscript{29}, male patients\textsuperscript{30} and progression disease to TKI therapy at the time of surgery\textsuperscript{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\textsuperscript{33}; however, recent reports showed evidence that surgical resection combined with TKI offered better prognosis than TKI monotherapy\textsuperscript{29,31,32}. As Bauer et al\textsuperscript{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\textsuperscript{26,29}.

**Other gastro-intestinal primary tumor liver metastases**

Pertaining to reports of liver resection for other gastro-intestinal 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\textsuperscript{10,16,34,35}. In the mean-

\begin{table}[h]
\centering
\caption{Summary of studies of each of which included \(\geq 40\) patients who underwent hepatectomy for liver metastasis from gastric cancer}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
Ref. & Year & Period & No. of patients & MST (mo) & 3-ysr (%) & 5-ysr (%) & Factors associated with worse overall survival \\
\hline
Ambi et al\textsuperscript{27} & 2001 & 1975-1999 & 40 & 12 & NR & 18 & Synchronous metastasis \\
Adam et al\textsuperscript{28} & 2006 & 1983-2004 & 64 & 15 & NR & 27 & NR \\
Cheon et al\textsuperscript{29} & 2008 & 1995-2005 & 41 & 18 & 32 & 21 & Multiple liver metastases \\
Takemura et al\textsuperscript{30} & 2012 & 1993-2011 & 64 & 34 & 50 & 37 & Serosal invasion of primary gastric cancer, maximum hepatic metastasis diameter \(> 5\) cm \\
Aizawa et al\textsuperscript{31} & 2014 & 1997-2010 & 53 & 27 & NR & 18 & Multiple liver metastases \\
Kinoshita et al\textsuperscript{32} & 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\textsuperscript{33} & 2015 & 1997-2011 & 53 & 13 & 14 & 9 & NR\textsuperscript{2} \\
Oki et al\textsuperscript{34} & 2015 & 2000-2010 & 69 & 41 & 31 & 42 & Multiple liver metastases, \(>2\) positive regional lymph node metastases of primary gastric cancer \\
\hline
\end{tabular}
\end{table}

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

\begin{table}[h]
\centering
\caption{Summary of studies of relatively large cohort of patients who underwent hepatectomy for liver metastasis from gastrointestinal stromal tumors}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
Ref. & Year & Period & No. of patients underwent hepatectomy & MST (mo) & 3-ysr (%) & 5-ysr (%) & 3-yPFS (%) & Factors associated with worse overall survival \\
\hline
DeMatteo et al\textsuperscript{35} & 2001 & 1982-2000 & 34\textsuperscript{1} & 39\textsuperscript{2} & 50\textsuperscript{3} & 30\textsuperscript{4} & 45\textsuperscript{5} & Interval from primary tumor diagnosis \(\leq 24\) mo\textsuperscript{6} \\
Nunobe et al\textsuperscript{37} & 2005 & 1984-2003 & 18 & 36 & 64 & 34 & NR & 3 (17\%) \\
Xia et al\textsuperscript{38} & 2010 & 2005 & 19 & 33 (mean) & 90 & NR & NR & 19 (100\%) \\
Turley et al\textsuperscript{39} & 2012 & 1995-2010 & 30 & Not reached at 5 yr & 68 & NR & NR & 27 (73\%) \\
Bauer et al\textsuperscript{40} & 2014 & Until 2011 & 104 & 96 & NR & NR & NR & > 84\% \\
Du et al\textsuperscript{41} & 2014 & NR & 19 & Not reached & NR & NR & NR & 88 (2-yr) \\
Seising et al\textsuperscript{42} & 2016 & 1999-2014 & 48 & 90 & 80 & 76 & 67 & 42 (88\%) \\
\hline
\end{tabular}
\end{table}

\textsuperscript{1}Including gastrointestinal sarcoma; \textsuperscript{2}Comparision to the non-operation group; \textsuperscript{3}Excluding two patients lost to follow-up; \textsuperscript{4}Results including resections of extrahaepatic metastasis. GIST: Gastrointestinal stromal tumor; MST: Median survival time; ysr: Year survival rate; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; NR: Not reported.
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-yr (%) | 5-yr (%) | Factors associated with worse overall survival |
|---------|------|------|--------|-----------------|---------|----------|----------|-----------------------------------------------|
| Peri-ampullary | De Jong et al.[46] | 2010 | 1993-2009 | 40 | 17 [23 (intestinal), 13 (pancreatobiliary)] | 18 | NR | Intestinal type (ampullary or duodenal) tumors |
| Ampullary | Adam et al.[4] | 2006 | 1983-2004 | 15 | 38 | NR | 46 | NR |
| Small bowel | Adam et al.[4] | 2006 | 1983-2004 | 28 | 58 | NR | 49 | NR |
| Pancreas | Adam et al.[4] | 2006 | 1983-2004 | 40 | 20 | NR | 25 | NR |
| Schiergens et al.[46] | | 2016 | 2003-2013 | 19 | 7 | 17 | NR | NR |
| Esophageal | Adam et al.[4] | 2006 | 1983-2004 | 20 | 16 | 32 | NR | NR |
| Ichida et al.[46] | 2006 | 2003-2005 | 5 | 13 | NR | NR | NR |

1As 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-yr (%) | 5-yr (%) | MDFS (mo) | Factors associated with worse overall survival |
|------|------|--------|-----------------|---------|----------|----------|----------|-----------------------------------------------|
| Pocard et al.[4] | 2000 | 1988-1997 | 52 | 42 | 49 | NR | NR | Disease free interval ≤ 48 mo (univariate) |
| Elias et al.[2] | 2005 | 1986-2000 | 54 | 34 | 50 | 34 | NR | Poor response to preoperative chemotherapy, R2, no repeat hepatectomy |
| Adam et al.[4] | 2006 | 1984-2004 | 85 | 32 | NR | 37 | 20 | Positive resection margin, disease-free interval < 24 mo |
| Adam et al.[4] | 2006 | 1983-2004 | 454 | 45 | NR | 41 | NR | ER-negative, disease progression before hepatectomy |
| Hoffman et al.[45] | 2010 | 1990-2008 | 41 | 58 | 68 | 48 | 34 | Lymph node metastasis in the primary tumor, absence of trastuzumab therapy, multiple liver metastases |
| Abbott et al.[46] | 2012 | 1997-2010 | 86 | 57 | NR | 44 | 14 | |
| Groeschl et al.[48] | 2012 | 1990-2009 | 115 | 52 | 52 | 27 | 22 | Non-hepatectomy, bone metastasis |
| Marianii et al.[48] | 2013 | 1988-2007 | 51 | 91 | NR | NR | NR | |
| Hoffmann et al.[48] | 2015 | 2003-2012 | 42 | 63 | NR | 53 | NR | |
| Sadot et al.[49] | 2016 | 1991-2014 | 69 | 50 | NR | 38 | 29 | |

1As a part of the report on-colorectal non-neuroendocrine liver metastases; 2Including 18 patients who underwent percutaneous ablation therapy; 3Comparison to the non-operation group; 4Comparison 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[10,40], and positive hepatic resection margin[38,39] in two studies; and the absence of repeat hepatectomy[38,41], 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[42]. As Sadot et al[43] 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 | MST (mo) (ocular/ cutaneous) | 3-ysr (%) | 5-ysr (%) | Factors associated with worse overall survival |
|------|------|--------|-----------------|-----------------|--------|--------|---------------------------------------------|
| Adam et al[26] | 2006 | 1983-2004 | 148 | 104/44 | 19/27 | NR | NR |
| Pawlik et al[27] | 2006 | 1988-2004 | 40 | 16/24 | 28 [29 (ocular)/24 (cutaneous)] | 62 (ocular)/48 (cutaneous) (2-yr) | 21 (ocular)/22 (cutaneous) |
| Mariani et al[28] | 2009 | 1991-2007 | 255 (R2 = 157) | 255/0 | 14 (27 mo after R0 resection) | NR | 7 |
| Mariani et al[28] | 2016 | 2000-2013 | 70 (including 13 concomitant with RFA) | 70/0 | 27 (hepatectomy), 28 (+RFA) | 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[29] | 2000 | 1982-1996 | 26 (including 9 second, 2 third resection) | 32 (R0 first resection), 21 (R1,2 resection) | 39 | 50 | Time to liver metastasis from the primary tumor diagnosis ≤ 24 mo |
| DeMatteo et al[30] | 2001 | 1982-2000 | 561 | 1 | 39 | 50 | Non-GIST |
| Pawlik et al[27] | 2006 | 1996-2005 | 53 (35Hx, 18RF + Hx, and 13RF), (including 36 GISTs) | 47 | 65 | 27 | Primarily leiomyosarcoma |
| Marudanayagam et al[31] | 2011 | 1997-2009 | 36 (including 5 GISTs) | 24 | 48 | 32 | Intervall from primary tumor diagnosis ≤ 24 mo, extrahepatic disease, positive margins |
| Groeschl et al[32] | 2012 | 1990-2009 | 98 | 72 | 60 | 32 | NR |
| Zhang et al[33] | 2015 | 2000-2009 | 27 | NR | NR | 46 | NR |

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], malignant 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[47]. 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[28,51], non-GIST[49], leiomyosarcoma[50], extrahaepatic 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
Overall 3- and 5-year survival rate of 54%-68% and 38%-62%, respectively, with median survival times of 33-142 mo (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 homogenous liver metastases.

Chemotherapy is highly effective in the treatment of testicular carcinoma; however, one-third of the patients either did not achieve complete responses or experienced relapses. 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.

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

---

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-yr (%) | 5-yr (%) | Factors associated with worse overall survival |
|-----------------------------|---------------|----------|----------|-----------------|----------|----------|----------|-----------------------------------------------|
| Renal cell carcinoma        | Adam et al[51]| 2016     | 1983-2004| 85              | 36       | NR       | 38       | NR                                            |
|                             | Thelen et al[52]| 2007     | 1988-2006| 31              | 48       | NR       | 54       | 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       | NR       | 47       | Synchronous metastases, R1,2 resection margin (univariate) |
| Gynecologic primary cancer  | Hatzaras et al[55]| 2012     | 1994-2011| 43              | Not reached | 62       | NR       | Disease-free interval ≤ 12 mo, extraportal disease (univariate) |
| Ovarian cancer              | Schiergens et al[56]| 2016     | 2003-2013| 28              | 50       | 68       | NR       | NR                                            |
|                             | Kamel et al[57]| 2011     | 1990-2010| 52              | 53       | 57       | 41       | NR                                            |
|                             | Merdith et al[58]| 2003     | 1976-1999| 26              | 26       | NR       | NR       | Interval from the primary diagnosis ≤ 12 mo, residual disease > 1 cm (univariate) |
|                             | Adam et al[59]| 2009     | 1983-2004| 65              | 98       | NR       | 50       | NR                                            |
|                             | Lim et al[60]| 2001     | 2001-2008| 14            | Not reached | 51       | Hematogenous liver metastasis < hepatic parenchymal metastasis from peritoneal seeding |
|                             | Neumann et al[61]| 2012     | 1991-2007| 41              | 42 (R0 resection) | NR       | R1,2 resection, pre-operative ascites, bilobar liver metastasis |
|                             | Niu et al[62]| 2012     | 2000-2011| 60              | 39       | NR       | 30       | R1,2 resection                                |
|                             | Kolev et al[63]| 2014     | 1988-2012| 27            | 56       | NR       | NR       | Interval from the primary surgery ≤ 24 mo, residual disease ≥ 1 cm |
|                             | Bacalbasa et al[64]| 2015     | 2002-2014| 31            | 16 (metastasis from seeding, 13 (hematogenous) | NR       | NR       | No significant risk factor |
| Testicular cancer           | Schiergens et al[65]| 2016     | 2003-2013| 24              | 33       | 43       | NR       | NR                                            |
|                             | Hahn et al[66]| 1999     | 1974-1996| 57              | 97 (2-yr) | NR       | NR       | NR                                            |
|                             | Adam et al[67]| 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 2a (n = 15), 3a (3) and 4 (2) cytoreduction operations; 5 Only risk factors that included patients undergoing palliative treatment were reported. MST: Median survival time; yrs: Year survival rate; NR: Not reported.

---

The nine largest studies pertaining to gynecological and testicular primary tumors are the first to advocate a favorable prognosis for hepatectomy in this field. 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

---

Overall 3- and 5-year survival rate of 54%–68% and 38%–62%, respectively, with median survival times of 33–142 mo (Table 9). The negative prognostic risk factors were the resection margin (R1,2), high-grade tumor, poor performance status, synchronous metastasis, short disease-free interval, and extrahepatic disease. 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. Factors associated with worse survival were shorter interval from the primary surgery, interval from the primary diagnosis < 12 mo, extraportal disease, lymph node status, residual disease > 1 cm, synchronous metastases, R1,2 resection margin, and bi-lobular hepatic metastasis (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.

Chemotherapy is highly effective in the treatment of testicular carcinoma; however, one-third of the patients either did not achieve complete responses or experienced relapses. 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.
required for the treatment of patients with diseases that are otherwise difficult to treat.

REFERENCES

1. Rees M, Tekkis PP, Welsh FK, O’Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008; 247: 125-135 [PMID: 18156932 DOI: 10.1097/SLA.0b013e31815e0c2e]

2. de Jong MC, Pulitano C, Clary BM, Reddy SK, Morgan P, Andriani O, Grondona J, Gil O, Raffin T, Ambiru S, Saiura A, Koga R, Yoshioka R, Yamamoto J. Long-term results of hepatic resection for non-colorectal, non-neuroendocrine liver metastasis. Hepatogastroenterology 2013; 60: 1705-1712 [PMID: 23933784 DOI: 10.5754/hge13078]

3. Saxena A, Chua TC, Sarkar A, Chu F, Lian W, Zhao J, Morris DL. Progression and survival results after radical hepatic metastasectomy of indolent advanced neuroendocrine neoplasms (NENs) supports an aggressive surgical approach. Surgery 2011; 149: 209-220 [PMID: 20674950 DOI: 10.1016/j.surg.2010.06.008]

4. Schwartz SI. Hepatic resection for noncolorectal nonneuroendocrine metastases. World J Surg 1995; 19: 72-75 [PMID: 7740813 DOI: 10.1007/BF0016982]

5. Harrison LE, Brennan MF, Newman E, Fortner JG, Piccardo A, Blumgart LH, Fong Y. Hepatic resection for noncolorectal, nonneuroendocrine metastases: a fifteen-year experience with ninety-six patients. Surgery 1997; 121: 625-632 [PMID: 9186462 DOI: 10.1016/S0039-6060(97)90050-7]

6. Elias D, Cavalcante de Albuquerque A, Eggenspieler P, Plaud A. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1,469 patients. Ann Surg 2009; 250: 440-448 [PMID: 19730175 DOI: 10.1097/SLA.0b013e3181b5393b]

7. Mayo SC, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, Celinski SA, Kooby DA, Staley CA, Stokes JB, Chu CK, Ferro P, Schulin RD, Choi MA, Aldrighetti L, Capussotti L, Pawlik TM. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Oncol 2010; 17: 3129-3136 [PMID: 20585879 DOI: 10.1094/s0-314-010-1154-5]

8. Saxena A, Chua TC, Sarkar A, Chu F, Lian W, Zhao J, Morris DL. Progression and survival results after radical hepatic metastasectomy of indolent advanced neuroendocrine neoplasms (NENs) supports an aggressive surgical approach. Surgery 2011; 149: 209-220 [PMID: 20674950 DOI: 10.1016/j.surg.2010.06.008]

9. Schwartz SI. Hepatic resection for noncolorectal nonneuroendocrine metastases. World J Surg 1995; 19: 72-75 [PMID: 7740813 DOI: 10.1007/BF0016982]

10. Wiez J, Blumgart LH, Fong Y, Jarnagin WR, Blumgart LH. Hepatic resection for non-colorectal, non-neuroendocrine liver metastases: an analysis of 64 macroscopically complete resections. Langenbecks Arch Surg 2012; 397: 951-957 [PMID: 22615045 DOI: 10.1007/s00423-012-0595-9]

11. Aizawa M, Nashimoto A, Yabusaki H, Nakagawa S, Matsuki A. Clinical benefit of surgical management for gastric cancer with synchronous liver metastasis. Hepatogastroenterology 2014; 61: 1439-1445 [PMID: 25513107]

12. Kinoshita T, Kinoshita T, Saiura A, Masaki M, Sakamoto H, Yamakawa T. Multicentre analysis of long-term outcome after surgical resection for gastric cancer liver metastases. Br J Surg 2015; 102: 102-107 [PMID: 25389030 DOI: 10.1002/bjs.9684]

13. Tiberio GA, Bocchi GL, Morganti P, Marrelli D, Marchet A, Cipollari C, Grattas L, Ministrini S, Vittirberga G, Donini A, Nitti D, Roviello F, Coniglio A, de Manzoni G. Gastric cancer and synchronous hepatic metastases: is it possible to recognize candidates to R0 resection? Ann Surg Oncol 2015; 22: 589-596 [PMID: 25190117 DOI: 10.1245/s10434-014-0186-8]

14. Oki E, Tokumaga S, Emyi Y, Kasumoto T, Yamamoto M, Fukuzawa K, Takahashi I, Ishigami S, Tsujii A, Higashi H, Nakamura T, Sae K, Shirabe K, Kakeji Y, Sakai K, Baba H, Nishimaki T, Natsugoe S, Mihara Y, Surgical treatment of liver metastasis of gastric cancer: a retrospective multicenter cohort study (KSCC1302). Gastric Cancer 2016; 19: 968-976 [PMID: 26260876 DOI: 10.1007/s11605-015-0530-z]

15. Markar SR, Mikhail S, Maitiezis G, Athanasia T, Mariette C, Sasaki M, Hanna GB. Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis. Ann Surg Oncol 2016; 23: 1092-1101 [PMID: 26797324 DOI: 10.1007/s10000-015-0530-z]

16. Takemura N, Saiura A, Koga R, Yoshioka R, Yamamoto J, Kokudo N. Repeat hepatectomy for recurrent liver metastasis from gastric carcinoma. World J Surg 2013; 37: 2664-2670 [PMID: 23963347 DOI: 10.1007/s00268-013-2190-7]

17. 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: 540-547, discussion 547-548 [PMID: 11163107]
January 20, 2017


cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. Surgery 2012; 151: 710-716 [PMID: 22825775 DOI: 10.1016/j.surg.2011.12.017]

41 Mariani P, Servois V, De Rycke Y, Bennett SP, Feron JG, Almubarak MM, Reyal F, Barangier B, Pierja YG, Salmon RJ. Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. Eur J Surg Oncol 2013; 39: 1377-1383 [PMID: 24126165 DOI: 10.1016/j.ejso.2013.09.021]

42 Sadot E, Lee SY, Sofocleous CT, Solomon SB, Gönen M, Peter Kingham T, Allen PJ, DeMatteo RP, Jarnangir WR, Hadis CA, D’Angelica MI. Hepatic Resection or Ablation for Isolated Breast Cancer Liver Metastasis: A Case-control Study With Comparison to Medically Treated Patients. Ann Surg 2016; 264: 147-154 [PMID: 26445472 DOI: 10.1097/SLA.0000000000001371]

43 Neuman HB, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? Cancer 2010; 116: 1226-1233 [PMID: 20101736 DOI: 10.1002/cancer.24873]

44 Pawlik TM, Zorzi D, Abdalla EK, Clary BM, Giershewald JE, Ross MI, Aloia TA, Curley SA, Camacho LH, Capussotti L, Elias D, Vauthey JN. Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease. Ann Surg Oncol 2006; 13: 712-720 [PMID: 16538410 DOI: 10.1245/ASO.2006.01.016]

45 Mariani P, Piperno-Neumann S, Servois V, Berry MG, Dorval T, Plancher C, Couturier J, Levy-Gabriel C, Lumbronso-Le Roux L, Desjardins L, Salmon RJ. Surgical management of liver metastases from uveal melanoma: 16 years’ experience at the Institut Curie. Eur J Surg Oncol 2009; 35: 1192-1197 [PMID: 19329272 DOI: 10.1016/j.ejso.2009.02.016]

46 Mariani P, Almubarak MM, Kollen M, Wagner M, Plancher C, Audollent R, Piperno-Neumann S, Cassoux N, Servois V. Radiofrequency ablation and surgical resection of liver metastases from uveal melanoma. Eur J Surg Oncol 2016; 42: 706-712 [PMID: 26968227 DOI: 10.1016/j.ejso.2016.02.019]

47 Agarwala SS, Eggermont AM, O’Day S, Zager JS. Metastatic melanoma to the liver: a contemporary and comprehensive review of surgical, systemic, and regional therapeutic options. Cancer 2014; 120: 781-789 [PMID: 24301420 DOI: 10.1002/cncr.28480]

48 Lang H, Nussbaum KT, Kaupel P, Frühnauf P, Flemming P, Raab R. Hepatic metastases from leiomyosarcoma: A single-center experience with 34 liver resections during a 15-year period. Ann Surg 2006; 231: 500-505 [PMID: 17049609 DOI: 10.1097/00000545-200604000-00007]

49 Pawlik TM, Vauthey JN, Abdalla EK, Pollock RE, Ellis LM, Curley SA. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. Arch Surg 2006; 141: 537-543; discussion 543-544 [PMID: 16753530 DOI: 10.1001/archsurg.141.6.537]

50 Marudanayagam R, Sandhu B, Perera MT, Bramhall SR, Mayer D, Buckels JA, Mirza DF. Liver resection for metastatic soft tissue sarcoma: an analysis of prognostic factors. Eur J Surg Oncol 2011; 37: 87-92 [PMID: 21163386 DOI: 10.1016/j.ejso.2010.11.006]

51 Zhang F, Wang J. Clinical Features of Surgical Resection for Liver Metastasis from Extremity Soft Tissue Sarcoma. Hepato-gastroenterology 2015; 62: 677-682 [PMID: 26897953]

52 Thelen A, Jonas S, Benecct C, Lopez-Hanninen E, Rudolph O, Neumann U, Neuhau P. Liver resection for metastases from renal cell carcinoma. World J Surg 2007; 31: 802-807 [PMID: 17354021 DOI: 10.1007/s00268-007-0685-9]

53 Staecker MD, Kruse J, Haseke N, Stadler T, Roosen A, Kari A, Stief CG, Jauch KW, Bruns CJ. Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. World J Urol 2010; 28: 543-547 [PMID: 20440505 DOI: 10.1007/s00345-010-0640-6]

54 Ruys AT, Tanis PJ, Nagtegaal ID, van Duijndijk P, Verhoef C, Porte RJ, van Gulik TM. Surgical treatment of renal cell cancer
A multi-institutional analysis of outcomes of liver-directed surgery for metastatic renal cell cancer. *HPB* (Oxford) 2012; 14: 532-538 [PMID: 22762401 DOI: 10.1111/j.1477-2574.2012.00495.x]

The role of liver-directed surgery in patients with hepatic metastasis from a gynecologic primary carcinoma. *World J Surg* 2011; 35: 1345-1354 [PMID: 21452068 DOI: 10.1007/s00268-011-1074-y]

Hepatic resection for metachronous metastases from ovarian carcinoma. *Gynecol Oncol* 2003; 89: 16-21 [PMID: 12694649 DOI: 10.1016/S0090-8258(03)00004-0]

The clinical significance of hepatic parenchymal metastasis in patients with primary epithelial ovarian cancer. *Gynecol Oncol* 2009; 112: 26-34 [PMID: 19010521 DOI: 10.1016/j.ygyno.2008.09.046]

Liver resection for ovarian cancer liver metastases as part of cytoreductive surgery is safe and may bring survival benefit. *World J Surg Oncol* 2015; 13: 235 [PMID: 26243426 DOI: 10.1186/s12957-015-0652-0]

Hepatectomy for NCNNLM
