Liver Resection for Non-Colorectal Liver Metastases – Standards and Extended Indications

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Summary
Background: Due to the uncertain benefit of liver resection for non-colorectal liver metastases (NCLM), patient selection for surgery is generally difficult. Therefore, the aim of this article was to propose standard and extended indications for liver resection in this heterogeneous disease collective. Methods: Review of the literature. Results: The myriad of biologically different primary tumor entities as well as the mostly small and retrospective studies investigating the benefit of surgery for NCLM limits the proposal of general recommendations. Only resection of neuroendocrine liver metastases (NELM) appears to offer a clear benefit with a 5- and 10-year overall survival (OS) of 74 and 51%, respectively, in the largest series. Resection of liver metastases from genitourinary primaries might offer reasonable benefit in selected cases – with a 5-year OS of up to 61% for breast cancer and of 38% for renal cell cancer. The long-term outcome following surgery for other entities was remarkably poorer, e.g., gastric cancer, pancreatic cancer, and melanoma reached a 5-year OS of 20–42, 17–25, and about 20%, respectively. Conclusion: Liver resection for NELM can be defined as a standard indication for the resection of NCLM while lesions of genitourinary origin might be defined as an extended indication.

Introduction
Secondary liver malignancies from various origins are the most common malignant hepatic diseases [1]. Among this very heterogeneous group, colorectal liver metastases (CLM) definitely display the lion’s share, and surgical resection appears to be the option of choice – with a well-demonstrated benefit regarding long-term survival [2, 3]. In contrast, concerning non-colorectal liver metastases (NCLM), the best suitable procedure is discussed controversially and varies enormously between the different primary tumor origins [4, 5]. The most common primary non-colorectal lesions are breast, gastrointestinal (esophageal, gastric, small bowel, and pancreato-biliary), neuroendocrine, renal, and genitourinary cancer, but also lung cancer, malignant melanoma, and soft tissue neoplasm (sarcoma) need to be taken into account [6]. Given this myriad of possible sources, it is problematic to estimate data regarding the overall benefit from hepatic resection since most studies report only small series with many different primary tumor entities. An exception to this is the surgical treatment of neuroendocrine liver lesion which has proven to be safe, providing a reasonable long-term survival similar to the resection of CLM [7]. In contrast, the benefit from the surgical treatment of metastases of other origin was generally considered as poor [8]. Therefore, defining a standard treatment is difficult; thus, regarding many tumor entities only some basic observations can be made. Nevertheless, since a few quality meta-analyses were published over the last years, reliable data to issue a treatment recommendation regarding some other entities is available. Accordingly, the aim of this article is to give an overview over the clinical outcome following the resection of various NCLM and to provide a guideline for standard and extended indications for hepatic resection of non-colorectal liver lesions.

Incidence of Liver Metastases
Most liver metastases are of colorectal origin. About 20–50% of patients either present with synchronous lesions or develop metachronous metastases after resection of the primary colorectal cancer [9, 10]. The benefit of surgical resection is widely accepted even in the case of recurrent disease and will not be further detailed [11]. Due to the hepatic first-pass effect of the intestinal venous
drainage through the portal vein, the liver is also a primary site for far-distant metastases of almost all other gastrointestinal cancers. These include gastric, pancreaticobiliary, small bowel, and neuroendocrine cancers mostly located in the pancreas or terminal ileum. Apart from neuroendocrine cancer, the presence of liver lesions was generally regarded as a palliative situation with poor overall prognosis although a metastasis to other body compartments might not have occurred.

Frequently seen are also metastases of breast cancer in advanced tumor stages as well as lesions originating from genitourinary cancers (ovarian, uterine, prostate, testicular, and renal cell cancer). Furthermore, malignant melanoma and soft tissue cancer such as sarcoma may spread into the liver. In these cases, hepatic metastasis is seen as a sign of systemic disease since tumor cells reach the liver through systemic circulation and not via the portal vein flow.

### Standard Indication

Since surgical resection of CLM is the best documented procedure so far, a distinct benefit from the resection of metastases of other entities should be compared to these results. Depending on the literature cited, resection for CLM provides 5-year survival rates between 25 and 60% and an individual survival of up to 15 years [12, 13]. Until now, only surgical treatment of neuroendocrine liver metastases (NELM) appears to offer similar long-term results. Neuroendocrine tumors (NET) arise mostly from the gastrointestinal and bronchopulmonary tracts and are rare lesions, though with an increasing incidence during the last years. Approximately 13% of patients display metastases at primary diagnosis while approximately 40% of the patients develop some during the further course [14]. Resection appears to be the only possible treatment in curative intent and is limited by the metastatic pattern in most cases. The following three metastatic types were described: i) type 1 with single lesion of any size, ii) type 2 defined by one metastatic bulk with smaller surrounding satellites and bilateral participation, and iii) type 3 with bilateral disseminated lesions and near total consumption of normal liver tissue [15]. In summary, only between 10 and 20% of these, and mostly the first two types, seem feasible for surgical resection. Within the last years, various publications examining long-term survival following liver resection of NELM were issued. Even though they vary in the number of patients included and the location of the primary lesion, an assessment of the benefit from surgical treatment is possible. In some studies, overall survival (OS) following resection amounted up to 9.6 and 10.5 years [7, 16], while in others a median 5- and 10-year survival of 59–75% and 31–45%, respectively, was described [17–19]. Recent studies evaluating the outcome following liver resection for NELM are summarized in table 1.

It is noteworthy that almost all of these studies report a high rate of early recurrence after 2 years, mostly regarding the liver. Within 5 years the overall rate of recurrence rose up to 94% [16, 18]. Negative predictors for early recurrence or impaired outcome were synchronous onset of NELM, presence of non-functional lesions, and extrahepatic tumor manifestations. The location of the primary tumor, administration of neoadjuvant regimes, histological grading, and, interestingly, the R status do not appear to have an impact on OS [16]. A matter of ongoing discussion is the effectiveness of orthotopic liver transplantation (OLT) as a curative treatment for unresectable hepatic metastases of NET. A large European multicenter study from 2013 displayed a reasonable 5-year OS and disease-free survival following OLT of 52 and 30%, respectively [20]. A large meta-analysis from 2015 even reported a 5-year OS of 70% [21]. Markers associated with poor prognosis were pancreatic or duodenal primary tumor, major surgery in the upper abdomen such as partial duodenopancreatectomy prior to OLT, hepatomegalia, and highly dedifferentiated lesions [20, 22]. The selection of patients eligible for OLT is mainly based on the inclusion criteria established by Mazzaferrato et al. [23], i.e. prior resection of the primary tumor located in the portal vein drainage area, well-differentiated tumors (Ki < 10%), and limitation of the disease to the liver with less than 50% tumor involvement. A follow-up of at least 6 months to assess the biological behavior and to document a stable disease was also considered reasonable but was not recommended by Fan et al. [21].

In summary, it appears certain that liver resection for NELM is safe and provides long-term survival with the handicap of risk for early recurrence. Nevertheless, resection for NELM should always be considered when technically possible and may be defined as a standard indication for liver resection due to NCLM.
Extended Indications

Although the overall value of surgical resection for non-colorectal and non-neuroendocrine (NCNN) liver metastases was generally considered as poor, numerous publications over the last years emphasized that selected patients may gain long-term survival from surgical therapy. However, since all of these case collectives were inhomogeneous regarding primary tumor location, individual treatment history, and staging at the time of liver surgery, it is difficult to reach a universal conclusion. Most challenging appears to be the appropriate selection of patients technically feasible for resection, taking into consideration that the indication should not only rely on surgical operability but also on the context of primary tumor disease, prior administered systemic treatment, and the response of the tumor to it.

Nevertheless, a case series of 273 patients from our center which investigated long-term survival following liver resection for NCNN liver metastases documented a 5-year OS of 28% [24], while various other studies reported rates of 19–39%, thus matching favorably with our results [6, 25, 26]. All of the studies showed that liver resection for NCNN liver metastases was safe and associated with similar rates of postoperative complications as seen in surgery for colorectal liver lesions. These overall results may not be satisfactory in general but might outrange non-surgical options depending on individual cases.

Most important in terms of prognosis and therefore defining the appropriate indication for resection is the primary tumor entity. Our own published data suggested that patients with liver metastases from breast and genitourinary cancer might benefit most from resection; the 5-year OS was 21–61%. On the contrary, liver resection for metastases from other gastrointestinal cancers showed worse outcomes – with a 5-year OS of only 10–20% [24]. The relatively encouraging results concerning the resection of liver metastases of the breast and of genitourinary origin are supported by other review analyses, with a 5-year OS of 20–60% for breast cancer [27, 28] and of 38–43% for renal cell cancer [29, 30].

The poor results for other than colorectal gastrointestinal tumor sites were reported in numerous studies elsewhere; the 5-year OS rates ranged from less than 15 to 30%. Some studies displayed that none of the patients even reached a 3-year survival [8, 31].

Table 2. Recent selected studies evaluating outcome after liver resection for NCNN liver metastases

| Primary tumor entity | Author | Year | Single vs. multi-center | Patients included, n | Median survival, months | One-year OS, % | Three-year OS, % | Five-year OS, % |
|----------------------|--------|------|--------------------------|----------------------|------------------------|---------------|----------------|---------------|
| Breast cancer        | Pocard et al. [42] | 2000 | single                    | 49                   | NR                     | 86            | 49             | NR            |
|                      | Yoshimoto et al. [43] | 2000 | single                    | 25                   | NR                     | 71            | 27             | 61            |
|                      | Vlastos et al. [44] | 2004 | single                    | 31                   | 63                     | 86            | NR             | 21            |
|                      | Sakamoto et al. [45] | 2005 | single                    | 34                   | NR                     | NR            | NR             | 21            |
|                      | Adam et al. [39] | 2006 | multi                     | 454                  | 45                     | NR            | NR             | 41            |
|                      | Kollmar et al. [46] | 2008 | single                    | 25                   | NR                     | NR            | NR             | 50            |
|                      | Lehner et al. [24] | 2009 | single                    | 57                   | 84                     | 52            | 30             | 30            |
|                      | Chua et al. [27] | 2011 | review                    | 553                  | 40                     | NR            | NR             | 40            |
| Renal cell cancer    | Alves et al. [47] | 2003 | single                    | 14                   | 26                     | 69            | 26             | NR            |
|                      | Adam et al. [39] | 2006 | multi                     | 85                   | 36                     | 40            | 38             | 38            |
|                      | Thelen et al. [30] | 2007 | single                    | 31                   | NR                     | 82            | 54             | 38            |
|                      | Lehner et al. [24] | 2009 | single                    | 29                   | NR                     | 73            | 47             | 22            |
| Gastric cancer       | Shirabe et al. [48] | 2003 | single                    | 36                   | NR                     | 64            | 26             | 26            |
|                      | Sakamoto et al. [45] | 2003 | single                    | 22                   | NR                     | 73            | 38             | 38            |
|                      | Koga et al. [35] | 2007 | single                    | 42                   | 34                     | 76            | 48             | 42            |
|                      | Cheon et al. [49] | 2008 | single                    | 58                   | NR                     | 75            | 32             | 21            |
|                      | Tiberio et al. [50] | 2009 | multi                     | 73                   | NR                     | 81            | 50             | 20            |
|                      | Lehner et al. [24] | 2009 | single                    | 22                   | NR                     | 80            | 10             | –             |
| Pancreatic cancer    | Adam et al. [39] | 2006 | multi                     | 40                   | 20                     | NR            | NR             | 25            |
|                      | Yamada et al. [51] | 2006 | single                    | 40                   | NR                     | 67            | 33             | 17            |
|                      | Gleisner et al. [52] | 2007 | single                    | 22                   | NR                     | 13            | 7              | NR            |
|                      | Lehner et al. [24] | 2009 | single                    | 12                   | NR                     | 30            | 18             | 8             |
| Melanoma (ocular vs. cutaneous) | Pawlik et al. [36] | 2006 | single                    | 20/20                 | NR                     | NR            | NR             | 21/0          |
|                      | Adam et al. [39] | 2006 | multi                     | 104/44                | 19/27                  | NR            | NR             | 21/22         |
|                      | Hsueh et al. [38] | 2007 | single                    | 24                   | 11                     | NR            | NR             | 39 (cutaneous) |
|                      | Lehner et al. [24] | 2009 | single                    | 20                   | NR                     | 63            | 42             | 21 (both types) |

NR = Not reported; OS = overall survival.
The worst outcome was described for lesions originating from esophageal, gastric, and pancreatic cancer; selected patients with metastases arising from gastric or duodenal cancer seem to show better outcomes [32, 33], albeit the data is not very conclusive in the case of gastric cancer. On the one hand, one review summarized that of 436 cases only 29 patients were alive after 5 years [34], while, on the other hand, a small report with obviously well-selected patients from Asia showed a 5-year OS of 42% [35]. Solitary lesions and low primary T stage were associated with a favorable prognosis.

Very variable are also the results following liver resection for metastases from malignant melanoma. Lesions originating from cutaneous melanoma were associated with impaired outcome due to the disseminated metastatic pattern and high risk of recurrence while metastases of the ocular type were considered as prognostically superior by some authors [36, 37]. However, the 5-year OS for both types mentioned was 7–36% [26, 38]. Taken together, in view of missing alternatives, resection was recommended as part of a multidisciplinary approach.

As already stated, all of the presented studies are limited by the lack of sizable patient numbers for the many different primary tumor entities, the heterogeneity of the individual cases, and the mostly retrospective approach. It must be speculated that all included patients were highly selected and did not represent an average treatment history. Therefore, a thorough review of the available data is required to classify the diverse entities into those feasible for liver resection and a reasonable benefit from it and into those who should be directed to multimodal treatment options. A great asset regarding this aspect was the large meta-analysis of 1,452 patients by Adam et al. [39], emphasizing that at least three different prognostic groups can be distinguished, which matches fairly well with the findings presented above.

The first group comprises tumors with the most benefit from resection and includes lesions of the breast as well as of genitourinary (testicular, ovarian, uterine, renal, and adrenal) and small bowel origin. The 5-year OS was >30% for these cases. The second group consisted of tumor origins from the foregut (gastric, duodenal, and exocrine pancreas) as well as both types of melanoma and displayed a 5-year OS of 15–30%. The last group showed a 5-year OS of less than 15% and comprised esophageal, lung, and head and neck primaries [39]. Table 2 provides a variety of selected studies exploring the outcome after resection for NCCN liver metastases.

In summary, in the case of lesions of the breast and of genitourinary origin, reasonable evidence for a benefit of liver resection is available, given that patients are thoroughly screened to exclude extrahepatic manifestations and hepatic surgery is embedded in a multimodal individual treatment concept. Hence, this group should define an extended indication for liver resection for NCLM.

Regarding liver metastases from other primaries the data is more inconclusive and difficult to interpret. Still, it appears that only highly selected patients might benefit from resection. In each individual case a careful reconsideration of the prior treatment history, the biological behavior of the tumor, and the effectiveness of alternative systemic chemotherapeutic therapies should be performed. As a result, an extended indication for resection in general cannot be proposed.

Conclusion

In conclusion, liver resection for NELM can be defined as a standard indication. Under distinct preconditions and based on thorough patient selection, liver metastases of breast and genitourinary primaries are extended indications for surgical hepatic treatment. In all other entities, hepatic resection should only be considered as a part of individual treatment concepts.

Disclosure Statement

The authors have no conflict of interest to declare.

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