LIVER RESECTION FOR NON-COLORECTAL, NON-ENDOCRINE LIVER METASTASIS

OSKAR KORNASIEWICZ, JOANNA LIGOCKA, MAREK KRAWCZYK
Department of General, Transplant and Liver Surgery, Warsaw Medical University
Kierownik: prof. dr hab. M. Krawczyk

Liver metastases of non-colorectal non-endocrine origin (NCNELM) are rare indications for resection. Even in major liver surgery units, NNCNELM constitute no more than 5% of all indications for resection. Such a small number is due to the fact that in the case of NCNELM, both primary and metastatic lesions are generally recognized in the advanced stages of the disease when not only metastases to the liver are present. Yet another important factor is the general belief that in the case of an advanced disease with the presence of liver lesions, surgical resection does not benefit patients.

In terms of survival, despite differences in cancer biology, patients with NCNELM are often compared with the results of surgical treatment for colorectal liver metastases (CLM), for which resection has been now widely recognized as the treatment of choice. Additionally, in the case of CLM, chemotherapy treatment has significantly improved over the last several years, leading to an increase in potentially radical liver resections and re-resections. This has led to a perspective where CLM are currently seen as a manifestation of the metastatic process with the possibility of effective surgical treatment. In Poland, the latest results of surgical treatment for CLM were presented by Dudek at al. with a 5-year survival of 47.6% (1). However resection of NCNELM has been only considered as a palliative treatment. On the other hand, the lack of effective chemotherapy for NCNELM leads to the conclusion that surgery is currently the only means of treatment which may lead to a potential cure.

Therefore the strategy of resecting NCNELM has been increasingly used as a part of oncological treatment. It has gained increasing acceptance only in the last several years, which has been largely the result of a paper published in 2006 by Adam et al., in which the authors demonstrated the value of surgical treatment on the long term survival of 1452 patients with NCNELM (2). Although the study had some drawbacks (the most serious problem was the fact that the data were collected as multicentre study over 20 years), to this day it remains the only work based on such a broad material. Most of the other published data on NCNELM resection present a relatively small number of patients, and even these works are burdened with a long period of data collection (tab. 1).

When analysing the value of surgical treatment for NCNELM, one should keep in mind that Five year survival is often sporadic in cases where resection was not performed.

The purpose of this review is to present the current state of knowledge on the surgical treatment of liver metastases of non-colorectal non-endocrine origin.

Melanoma liver metastasis

Metastasis to the liver in melanoma depends on primary location, with ocular and skin metastasizing in 80% and 20% of patients, respectively. Typically, lesions are bilobar involving all segments of the liver with survival not exceeding 6 months (3). To improve
Liver resection for non-colorectal, non-endocrine liver metastasis

Long term prognosis, in some selected cases liver resection can be considered, with five-year survival at 20.5% according to Pawlik et al., 21% in a French study, and up to 36% (median – 39 months) as observed by Groeschl et al. (5, 2, 6). Risk factors include female gender, young age, short time between diagnosis of the primary tumor and metastases, extrahepatic dissemination and R0 resection margin, negative PET scan and no other additional comorbidities (5, 6). According to Adam et al. predictors of survival were: metastases restricted to liver, tumors smaller than 5 cm, R0 resection, and greater than 12 months between primary and liver metastasis (2). It should be noted that melanoma of the skin and eyeball are two different diseases with different predisposing risk factors and affinity to liver. There is a 90% risk of liver metastasis confined to the liver in ocular, and approximately 1% in skin melanoma (8). This means that liver limited dissemination is typical for uveal melanoma, whereas intra and extra-hepatic is more commonly associated with skin melanoma (bone, lung). In both cases, the prognosis is unfavourable due to a lack of effective chemical treatment. Nevertheless, liver resection remains the only effective treatment in any melanoma case, but only in the absence of extra-hepatic dissemination.

Breast cancer liver metastasis

In the progression of breast cancer up to nearly 60% of women will have liver metastases. In 20% of these patients, the metastases occur within 5 years after resection of the primary, and they are usually multiple, bilobar lesions. Liver limited lesions are present in a relatively small number of patients (approx. 4-8%), of which only approx. 10% may be eligible for liver resection. Liver metastases are the main cause of death in this group of patients, and five-year survival does not exceed 8% (9). According to Belda et al. five-year survival reached 23% in patients suitable for liver resection and up to 61% in data presented by Vlastos et al. (11, 12). The largest group (115 patients), as described Groeschl et al., showed a 31% five-year survival rate (6). Surgery is not a definitive treatment, as indicated by the presentation of liver recurrence in 50% of patients an average of 22 months after resection (10) (tab. 2). However, in selected cases a second liver resection can be considered.

Data in the literature suggest that, contrary to common opinion, extrahepatic changes are not the most important prognostic factor in this group of patients (13). Furthermore, the extent of primary tumor infiltration, metastasis to regional lymph nodes, the extent of liver resection, number or size of the metastasis also seem to have no effect on survival (14). Also noteworthy is the response to chemotherapy. Patients in which disease progression occurred during chemotherapy did not survive five years compared with 41% five-year survival in patients who showed stabilization or regression on chemotherapy (15). It is therefore considered that the response to chemical and hormonal therapy is an important prognostic factor. In a selected group of patients, the inclusion of surgery as a part of the treatment increased five-year survival rate to as much as 40% (16). Therefore, more and more often it is now considered

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Five-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elias (23)</td>
<td>1998</td>
<td>120</td>
<td>36%</td>
</tr>
<tr>
<td>Weitz (4)</td>
<td>2005</td>
<td>141</td>
<td>28%</td>
</tr>
<tr>
<td>Ercolani (7)</td>
<td>2005</td>
<td>142</td>
<td>34%</td>
</tr>
<tr>
<td>Adam (2)</td>
<td>2006</td>
<td>1452</td>
<td>36%</td>
</tr>
<tr>
<td>Lendoiro (51)</td>
<td>2007</td>
<td>106</td>
<td>19%</td>
</tr>
<tr>
<td>O’Rourke (52)</td>
<td>2008</td>
<td>102</td>
<td>39%</td>
</tr>
<tr>
<td>Ercolani (53)</td>
<td>2009</td>
<td>134</td>
<td>40%</td>
</tr>
<tr>
<td>Lehner (54)</td>
<td>2009</td>
<td>242</td>
<td>28%</td>
</tr>
<tr>
<td>Groeschl (6)</td>
<td>2011</td>
<td>420</td>
<td>31%</td>
</tr>
</tbody>
</table>

* multicenter study

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Five-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubrano (55)</td>
<td>2008</td>
<td>16</td>
<td>33%</td>
</tr>
<tr>
<td>Carali (13)</td>
<td>2008</td>
<td>12</td>
<td>33%</td>
</tr>
<tr>
<td>Adam (2)</td>
<td>2006</td>
<td>85</td>
<td>37%</td>
</tr>
<tr>
<td>Elias (23)</td>
<td>2003</td>
<td>54</td>
<td>34%</td>
</tr>
<tr>
<td>Meloni (56)</td>
<td>2009</td>
<td>87</td>
<td>27%</td>
</tr>
<tr>
<td>Belda (11)</td>
<td>2010</td>
<td>21</td>
<td>23%</td>
</tr>
<tr>
<td>Vlastos (12)</td>
<td>2004</td>
<td>31</td>
<td>61%</td>
</tr>
<tr>
<td>Groeschl (6)</td>
<td>2011</td>
<td>115</td>
<td>31%</td>
</tr>
</tbody>
</table>
to surgically treat liver metastases as part of the oncological treatment algorithm for this group of patients.

Metastasis from the digestive tract: esophagus, stomach, pancreas, small intestine

Regardless of the histological type of the primary esophagial tumour, on average metastases will be present in 25% of patients 20 months after primary resection. The liver is one of the most common sites where lesions are multiple and bilobar, and in any case of secondary lesions, the three-year survival rate drops to zero (17). Synchronous liver metastases, which affect one third of patients, are now recognized as an absolute contraindication for surgical treatment (17, 18). Metachronous metastases are rarely limited only to the liver (7). In the literature, there are few cases described of liver resection due to esophageal cancer with five year survival approximately 10% (2). Given the poor long-term prognosis for patients after metachronous esophageal liver metastases, generally resection of liver secondaries is not advocated beyond a symbolic number of patients of whom the tumor was stabilized on chemotherapy.

The liver is the site where most often distant gastric cancer metastases occur, constituting 5 to 9% of all tumour metastases (19). The most common lesions are followed by other extra-hepatic dissemination sites. Patients with synchronous tumours limited to the liver have a significantly worse prognosis than patients with metachronous diseases (20). Only 16% of patients with gastric cancer metastases confined to the liver were suitable for resection or ablation according to Dittmar et al. (21). In other study, Cheon et al. showed that only 2.2% of patients with gastric cancer had liver resection (22). There are several hundred cases of hepatic resection described in the literature up to date, including several European articles (23, 24) (tab. 3), with the largest European group (n = 64) presented by Adam et al. (2). In a retrospective review, Kerkar et al. presented five-year survival at 13.4% (25). Japanese studies show a higher five year survival rate of 32%, of which three-fourths of patients had liver recurrence during follow up (26). Adam et al. observed five-year survival in 27% of patients with an average survival time of 15 months (2). Prognostic factors influencing survival are as follows: R0 resection, a limited number of deposits, and metachronous lesions (26). Metastases in the peritoneum or other distant organs are considered to be contraindications for liver resection (19, 21, 22). Any anticipated resection of liver metastases should be part of a multidisciplinary treatment and only after stabilization of the disease during chemotherapy and for liver limited metastases (25). Therefore, currently the resection of metastatic liver lesions of gastric cancer cannot be regarded as a universally recommended procedure.

In the literature there are sporadic information for pancreatic cancer patients who underwent simultaneous pancreas and liver resection for synchronous liver metastases (27). A relatively common indication for resection is a metachronous lesion after stabilization of the disease on chemotherapy (28). A multicenter study in France with the largest group of patients (n=40) showed a 20-month median survival (2) (tab. 4).

Currently, there are no recommendations for the surgical treatment of liver metastases of pancreatic cancer. Patients without evidence of progression during chemotherapy could be considered for surgery only on the assumption of radical surgical treatment. Such a strategy in some cases may result in improved long term survival.

Cancer of the small intestine is one of the rarest gastrointestinal tumors. The liver is typically the second location, after peritoneum to develop secondary lesions (29). Surgical treatment of liver metastases is described in

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Five-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheon (22)</td>
<td>2008</td>
<td>58</td>
<td>21%</td>
</tr>
<tr>
<td>Thelen (19)</td>
<td>2008</td>
<td>24</td>
<td>10%</td>
</tr>
<tr>
<td>Tsujimoto (26)</td>
<td>2010</td>
<td>17</td>
<td>32%</td>
</tr>
<tr>
<td>Dittmar (21)</td>
<td>2011</td>
<td>15</td>
<td>27%</td>
</tr>
<tr>
<td>Garancini (57)</td>
<td>2011</td>
<td>21</td>
<td>19%</td>
</tr>
<tr>
<td>Yang (58)</td>
<td>2012</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>Kerkar** (25)</td>
<td>2010</td>
<td>436</td>
<td>13.4%</td>
</tr>
</tbody>
</table>
Liver resection for non-colorectal, non-endocrine liver metastasis

The literature exceptionally rarely (30). This is due to the fact that the primary lesion is often diagnosed in an advanced stage of the disease with multiple liver metastases (30). Adam et al. proposed, in the case of metachronous lesions, the use of chemotherapy before liver resection, in order to select patients who are likely to obtain the potential benefits from such an operation (2).

Metastases from renal cell carcinoma, testes and prostate

Renal cell carcinoma liver metastases are present in approximately 19% of patients with stage IV and typically are associated with extra-hepatic dissemination (31). There is a small group of approx. 5% of patients with dissemination limited to the liver (8). By 2012, there were 14 studies describing a series of more than 10 patients. Aloia et al. observed five-year survival at 40% compared to 10% in patients without resection (33). Other data shows a five-year survival rate of 62.2% compared to 29.3% for patients who did not undergo resection (34). Thelen et al. showed five-year survival at 38.9% (35). In a study by Hatzarasa et al., 41.9% of patients had a recurrence an average of 15.5 months after resection (36). However, in the absence of effective treatment by radiotherapy, chemotherapy and immunotherapy for metastatic liver lesions, resection has been the only way to increase long term survival. Recent reports describe successful treatment of liver lesions with Sunitinib, which along with resection potentially should provide the additional benefit of prolonged survival (32). Prognostic factors affecting survival are: metachronous type of metastases, R0 resection, male gender, tumor <5 cm, and primary tumor in the left kidney (33, 35, 36).

Testicular cancer is the most common solid tumor in a population of young men. Due to significant chemosensitivity and radiosensitivity, up to 80% of patients have a chance of a full recovery (37). Surgical treatment is selectively reserved only for remnant lesions left after chemotherapy as it is the only effective way to confirm the efficacy of the treatment (38). No proven benefits of resection of liver metastases in the event of resistance to chemotherapy have been shown. In cases of complete response to chemotherapy a 5-year survival rate of 45% was achieved (21, 22).

Metastatic prostate cancer in the liver usually occurs sporadically as associated with extensive dissemination. Adam et al. presented only four cases of liver resection in relatively young patients (2). One should note that this is a cancer of older men with associated comorbidities, therefore the decision of possible liver resection should be undertaken with extreme caution.

Metastases derived from the reproductive system: carcinoma of the ovary and uterus

Despite an encouraging 35% five-year survival rate after liver resection for metastatic cancers of the reproductive system, it is still a rare indication for resection. Ovarian cancer is the most common cancer metastizing to the liver. Nearly 80% of the cases of liver lesions are associated with other extra-hepatic dissemination, particularly that of the peritoneum. Resection of liver metastases only potentially improves long term survival (2, 39, 41). In the case of diffuse, extrahepatic lesions, indications for liver resection are less convincing and not well defined (42). Often peritoneal lesions “mimic” hepatic tumors, which can be verified only intraoperatively. Prognostic factors influencing the survival are: time greater than 12 months between initial primary surgery and liver resection, complete surgical resection, R0 resection and extrahepatic deposits (39, 41). Currently, there is little doubt that resection should be part of a multi-stage and multi-disciplinary treatment (2, 39, 41, 42).

Uterine cancer rarely metastasizes to the liver, therefore, there is little literature de-

---

Table 4. Publications regarding survival rates following liver resection due to pancreatic cancer metastases

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Five-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berney (59)</td>
<td>1998</td>
<td>34</td>
<td>27%</td>
</tr>
<tr>
<td>Adam (2)</td>
<td>2006</td>
<td>40</td>
<td>25%</td>
</tr>
<tr>
<td>Yamada (60)</td>
<td>2006</td>
<td>33</td>
<td>17%</td>
</tr>
<tr>
<td>Gleisner (61)</td>
<td>2007</td>
<td>22</td>
<td>–</td>
</tr>
<tr>
<td>Hartwig (62)</td>
<td>2011</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>Klein (63)</td>
<td>2012</td>
<td>22</td>
<td>–</td>
</tr>
</tbody>
</table>
scribing such a condition (2, 7, 23). Surgical treatment may be beneficial in the case of single, liver limited deposits, with time greater than 24 months between resection of the primary and liver metastases along with chemosensitivy of the secondary tumours. Extrahepatic lesions are, however, a contraindication for liver resection (43). The largest group of patients described Adam et al. showed a five-year survival rate of 35% (2).

Lung cancer liver metastases

Stage IV lung cancer includes liver metastases with an average survival time of 7 to 11 months (44). 20-50% of patients with lung cancer develop metastases to the liver and other organs during the natural course of the disease, which greatly limits the effects of surgical treatment (44). The current published data all involve small groups of patients with incidental five year survival rates (24) (tab. 5). In the multi-center French study five year survival was 8% with an average survival of 7.4 months (2). Despite such unsatisfactory results, it seems that in patients who respond to chemotherapy (and thus in which cancer stabilizes), resection of liver metastases may in some cases prolong survival.

Table 5. Chosen publications concerning results of liver resection due to lung cancer metastases

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Five-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groeschl (6)</td>
<td>2012</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Adam (2)</td>
<td>2006</td>
<td>34</td>
<td>8%</td>
</tr>
<tr>
<td>Benevento (64)</td>
<td>2000</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

it is performed very rarely, although liver resection may affect long term survival. Adam et al. presented five-year survival at 65.5%, and in the event of liver recurrence, 1/3 of patients will have another liver resection performed (2). Yet, other results presented by American authors showed five-year survival at 29%, with almost a 100% incidence of tumour recurrence (49). For hormonally active tumors, resection seems to be the treatment of choice in order to control clinical symptoms rather than to extend lifespan. Hormonally active tumor is also the most important predictor of better prognosis (50). In contrast, indication for liver resection of hormonally silent tumors is poorly defined. In summary, the complete removal of liver lesions may extend survival in selected group of patients and should always be prudent in the case of hormonally active tumors.

Summary

NCNELM belong to a heterogeneous group of tumors of different primary sites rarely limited only to the liver. The majority of patients have bilobar hepatic and extrahepatic dissemination. The undeniable success of CLM resection and increase in five-year survival has led to cautious optimism in relation to the surgical treatment of NCNELM. Compared with colorectal liver metastases, NCNELM treatment is much less understood particularly in regards to the role and place of liver surgery in multidisciplinary treatment. NCNELM resection has not been widely recognized and a well established standard of care, so there has not been accepted criteria for eligibility of these patients for liver resection.

Despite evidence for the positive impact of resection on a long term survival, surgical treatment of NCNELM still remains a matter
of surgical debate. The number of publications has been increasing over the last several years concerning this subject, however the available data is retrieved from retrospective studies involving insignificant numbers of patients in most of the instances. The available data however show that resection is a safe procedure and the number of complications is not greater than that of hepatic resection for CLM. The 5-year survival rate of 19 to 40% largely depends on the criteria or indications applied for resection as well as primary tumor biology and chemosensitivity.

Up to date experience clearly shows that there is a group of patients in whom resection may prolong survival, but how to define this group is still unclear. The only significant group of patients with NCNELM (without sarcomas) in Polish literature has been described recently with 5 year survival rate at 42.3% (65).

In order to obtain optimal long-term results as well as a level of long term survival similar to that of CLM, the decision for surgery should be based on the following criteria: extended time between primary tumour and liver metastases, a single hepatic lesion, complete radical surgery, sensitivity to chemotherapy and histopathological type of adenocarcinoma. Regardless of the proposed selection criteria for resection, the primary goal of surgery should be to perform a safe procedure with complete removal of all lesions in the liver. The decision about surgery should be based on the objective of only complete radical treatment, avoiding palliative resection and cases with extrahepatic dissemination. For this purpose, it is important to take a multi-disciplinary approach always involving the surgeon with the careful „case by case” assessment of the potential value of liver metastases resection.

REFERENCES

Liver resection for non-colorectal, non-endocrine liver metastasis: have we made progress? World J Surg 2006; 30: 872-78.
54. Lehner F, Ramackers W, Bektas H et al.: (Liver resection for non-colorectal, non-neuroendocrine liver metastases—is hepatic resection justified as part of the oncosurgical treatment?). Zentralbl Chir 2009; 134: 430-36.

Received: 1.09.2014 r.
Adress correspondence: 02-097 Warszawa, ul. Banacha 1a
e-mail: oskar.kornasiewicz@wum.edu.pl