Chapter 8

Surgical Indications, Timing, and Strategy in Non-colorectal Liver Metastases

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Abstract

Taking into consideration all primary solid tumors, the liver represents the most common site involved in distant metastasization, also due to its important blood reception from the majority of digestive organs. Despite the abundant literature and guidelines about colorectal liver metastases, there is still great debate about the treatment strategy in the case of non-colorectal ones. Therefore, in this chapter, we reviewed the treatment strategy and surgical indications for the most frequent non-colorectal liver metastases. In the case of neuroendocrine hepatic secondaries, the literature suggests that surgery should be always considered for patients with resectable hepatic disease, as this treatment results more likely to offer the best long-term outcome. For what concerns liver metastases from gastric cancer, surgical approach should always be undertaken if indications are appropriate, after a multidisciplinary discussion to plan an adequate multidisciplinary adjuvant treatment, a proper patient selection, and the exclusion of additional secondary tumors or extrahepatic metastases. Taking into consideration liver secondaries from breast cancer and their chemosensitivity, in the absence of brain and lung lesions, it can be considered a space for liver surgery, especially in the case of single lesions or a maximum of two lesions with dimensions within 3 cm. However, as the number of cancer survivors is progressively increasing and, with it, the number of patients affected by non-colorectal liver metastases, further randomized controlled trials are required in order to better define the benefit of hepatic surgery in these kinds of patients.

Keywords: Non-colorectal liver metastases, Non-colorectal hepatic metastases, Metastatic neuroendocrine tumors, Metastatic breast cancer

1. Introduction

Cancer metastasization is a highly selective, sequential, interdependent, nonrandom process which causes transient or permanent changes in different genes at the DNA and/or mRNA, creating a complex phenotype which favors the survival of a population of tumor cells within an organ environment, distant from the primary tumor [1, 2]. This kind of complex process usually requires many years in order to complete the great series of cumulative DNA changes which consent neoplastic cells to metastasize. As the primary tumor growth may be very slow and the metastasization process does not directly depend on primary tumor size, we can observe two kinds of metastases based on the timing of their diagnosis: synchronous metastases are defined as secondary lesions diagnosed within the first year after primary tumor diagnosis, although this time, interval may vary in the literature between six months and one year, while metachronous metastases are usually diagnosed after one year from the primary tumor diagnosis.

Taking into consideration all primary tumors, the liver represents the most common site of the distant metastases. This particular affinity for distant metastases may have different explanations. First, it may be attributable to the site specificity patterns of neoplastic cells from various primary cancers, which found the liver as the adequate soil where to seed their circulating neoplastic cells [3, 4]. Furthermore, the liver receives 30% of the whole cardiac output, second only to the kidney for the quantity of blood which every day will perfuse its parenchyma, and is consequently more susceptible to neoplastic cell attachment. Moreover, anatomical or mechanical considerations, such as the efferent venous blood stream or the loco-regional lymphatic drainage, may be strongly responsible for this preference in the metastasization site [5]. In fact, most intra-abdominal cancers, and in particular those which originated in the digestive tract, result in having a great affinity for liver metastasization.

In spite of the great progresses of surgical techniques against the primary tumors, as well as the improvement of adjuvant therapies, metastatic disease continues to be the greatest challenge for the medical and the surgical oncologists. In fact, metastases are well recognized as being the major cause of death among neoplastic patients, and the prognosis of patients affected by unresectable liver metastases is very poor. However, although once metastatic malignancies were commonly considered as a terminal neoplastic stage, nowadays, many different therapeutical options have been introduced in order to provide a safe and efficient treatment for these kinds of patients and improve both their quantity and quality of life [6–9].

Despite the abundant literature about colorectal liver metastases and the existence of a great number of guidelines about this argument, there is still great debate about the treatment strategy in the case of non-colorectal ones and controversies especially about the management of rare liver secondaries. On the other hand, a recent review about non-colorectal non-neuroendocrine liver metastases demonstrated surgery to be a benefit for these kinds of metastatic patients, especially for those affected by primary testicular, ovarian, and renal cell cancers but also for women with isolated breast cancer metastases to the liver [10].

Obviously, patients affected by rare hepatic metastases should be conveyed into bigger and more experienced centers, which could be able to more appropriately treat this kind of disease. However, metastatic patients are always more numerous – thanks to the improvement of chemotherapy and the introduction of targeted biological drugs – and

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deserve as many chances of treatment as possible in order to continue their long battle against cancer. In this chapter, we will then discuss indications and timing of surgery in cases of the most frequent non-colorectal liver metastases.

2. Liver Metastases from Neuroendocrine Tumors

Neuroendocrine tumors (NETs) include a heterogeneous group of neoplasms with different origins and biological behaviors [11–13]. They are commonly distinguished into two classes based on their primary origin: pancreatic neuroendocrine tumors (also known as islet cell tumors) and gastrointestinal neuroendocrine tumors (also known as carcinoids) [14–16].

The widely promulgated benignity of these neoplasms has been more times brought into question, due to the high prevalence of distant metastases and recurrences, and the current literature recognizes nowadays their malignant potential [12, 17–24]. In particular, the recent classifications of the 7th American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) 2009 and of the European Neuroendocrine Tumor Society (ENETS) 2006, associated with the WHO classification 2010, classified NETs into well-differentiated neuroendocrine tumors (low and intermediate grade based on the Ki67 labeling index, also named NET-G1 or carcinoid and NET-G2, respectively) and into the group of neuroendocrine carcinomas (high grade, poorly differentiated, also named NEC) [21].

Despite their rarity, liver metastases from NETs are not an infrequent finding, because they are usually characterized by a very slow growth pattern and diagnosed in advanced stages [9, 15, 25–29]. In particular, NETs present with liver metastases in even the 50–75% of cases [30–32]. In an analysis of Modlin and colleagues on 13,715 patients, synchronous distant metastases were already evident in 12.9% of patients with gastrointestinal NETs, whose 5-year overall survival rate resulted 67.2% [13].

The occurrence of hepatic secondaries is one of the most important prognostic factor for survival [9, 21, 33, 34]. In fact, although for patients with unresectable liver disease, biotherapy with somatostatin analogues, peptide-mediated radioreceptor therapy, transarterial chemoembolization, selective intra-arterial radiotherapy, or new molecular target-directed therapy can be employed [16, 35, 36], these therapies are considered as palliative.

The role of liver surgery for patients with liver metastases from gastrointestinal NETs remains to be an argument of great debate. In particular, the very small number of patients affected by NETs explains the lack of randomized control trials in order to better define the role of surgery in these rare cases. Moreover, the usually inert growth of NETs and their long-term natural history make even more difficult to assess the real effectiveness of hepatic surgical approach on their overall survival. Furthermore, it is well known that in most patients, neuroendocrine liver metastases recur after hepatic resection in up to 70–94% of cases at 5 years [21, 24, 25, 33, 37–39], the liver is the most common site of progression of disease (69%) [35], and data on repeat liver directed surgery for recurrent disease have been extremely limited and controversial [36]. In particular, in a study of Saxena and colleagues, most patients with hepatic metastases from NETs experienced treatment failure after liver resection. In particular, 57 patients (79%) developed disease progression at a

median time of 23 months, and the liver represented the most common site of progression of disease (69%) [23]. In another multi-institutional study on 339 patients, Mayo and colleagues demonstrated that the majority of liver metastases from NETs came from carcinoid (53%) and, at 5 years after surgery, their recurrence rate was 94% [38]. Therefore, the true curative role of liver-directed surgery results is still very questionable.

A recent meta-analysis performed on five studies, considering 374 patients affected by NETs liver metastases treated in a conservative manner and 161 treated with liver surgery, demonstrated a significant increased survival in the group of patients treated with surgical hepatic resections HR 0.45 (CI.95 0.34–0.60) in comparison to conservative treatments and to embolization HR 0.34 (CI.95 0.21–0.55) [40]. All considered studies showed an increased survival in the groups treated with complete surgical resection of liver metastases, but none of the included studies were randomized so that the clinical evidence was low [21, 41, 42].

A systematic review considering 29 studies (between 1980 and 2009) found 5 years OS of 70.5% (range 31–100%) and a 5-year progression-free survival of 29% (range 6–66%) [43]. Histological grade, extrahepatic disease, and macroscopically incomplete resection of liver metastases were associated with poor prognosis. In another multi-institutional study evaluating 339 patients, Mayo et al. demonstrated at multivariate analysis that synchronous disease, nonfunctional NET hormonal status, and extrahepatic disease were the most important predictive factors of worse survival [36]. Concerning other prognostic parameters for primary NETs and liver metastases, Katz et al. demonstrated that the robust presence of tumor-infiltrating lymphocytes is a significant predictor of outcome [44]. Other recent articles confirmed surgical therapy to be the most efficient approach against solitary hepatic metastases [7, 8, 14, 22, 23, 33, 34, 40, 45, 46], with a potential curative resection of liver secondaries can be undertaken in 13.7 to 24.5% of patients with metastatic NETs [47–49], and a significant reduction of carcinoid symptoms [43], but the majority of studies focused exclusively on resection rather than combined-modality approaches with ablation or chemotherapy.

Taking into consideration our institutional cases of liver metastases from NETs, including 52% of synchronous metastases and 48% of metachronous ones, the overall survival of patients who underwent hepatic resections and OLT resulted, respectively, in 44.9% (95% CI 26.0–77.7%) and 50% (95% CI 12.5–100.0%) at 5 years [45]. The median number of resected hepatic metastases was 3. Surgical radicalness (R0) was reached in 84% of cases. Recurrences happened in 60% of patients, among which, 66.7% were intrahepatic and 33.3% extrahepatic. Postoperative complications affected 12% of patients but required reintervention in a single case.

In our opinion, surgery should be always considered for patients with resectable hepatic disease, as this treatment results more likely to offer the best long-term outcome. All patients should be considered for curative surgical treatment, but also palliative resection of liver metastases can be suggested. The advantage that can be potentially achieved with surgery is that of removing all gross diseases. In the future, new clinical and biological prognostic factors could be of help for the better identification of those patients who might benefit from hepatic surgical therapy.

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3. Liver Metastases from Gastric Cancer

Gastric cancer is the fourth most common cancer worldwide [50] and the second cause of cancer-related death worldwide [50]. Despite the significant reduction of gastric cancer incidence in the last 20 years, we observed an increase of advanced stages at diagnosis [51]. In Western Europe and Anglo-Saxon world, the incidence of hepatic metastases from gastric cancer during the course of the disease results about 30%-50%, including both synchronous and metachronous metastases [52, 53]. In particular, at the time of diagnosis, 35% of patients present with evidence of distant metastases, and 4% to 14% have metastatic disease to the liver [54–74], whereas metachronous metastases after curative gastrectomy are detected in up to 25–30% of patients, 80% of which appear within the first 2 postoperative years.

Surgical treatment of hepatic metastases from gastric cancers remains to be an argument of great debate [72, 75–78]. In fact, although many studies observed no survival difference among patients submitted or not to liver surgery, in selected cases, an aggressive treatment can achieve unexpected results [65–68, 70, 73, 74, 79–85]. Moreover, surgical approach is not always possible, due to multiple hepatic metastases or the presence of extrahepatic secondaries [52, 53], and only 0.4 to 1% of metastatic gastric cancer patients result in being eligible for radical surgery [54, 56, 57, 86].

Resection of liver metastases from gastric cancer was initially indicated in patients with synchronous metastases who have no peritoneal dissemination or other distant metastases and in those with metachronous metastases without any other recurrent lesion [68] and only if a complete resection of the metastases can be achieved without compromising postoperative liver function [70]. Thereafter, Roh and colleagues supported surgery indication only in cases of metastases in one lobe of the liver without peritoneal dissemination, hilar node metastases, or distant metastases [64]. Recently, in accordance with these findings, the Japanese Gastric Cancer Association revisited its treatment guidelines, which in the case of stage IV gastric cancer recommend only chemotherapy, radiation, palliative surgery, and best supportive care [87], in favor of surgery with curative intent for potentially resectable M1 disease, including patients with resectable hepatic metastasis, positive cytological examination of peritoneal washes, or swollen nodes in the para-aortic region [88].

Unfortunately, if we review the current literature, hepatectomy was indicated in only 0.4% to 1% of gastric cancer patients with liver metastases, because most hepatic metastases from gastric adenocarcinoma are multiple, bilateral, and combined with peritoneal or lymph node metastases, which directly invade adjacent organs, so that finally very few patients result as good candidates for liver surgery [89]. Moreover, surgical indications for liver metastases of gastric origin must be carefully determined because of the biological, clinical, and pathological aggressiveness of the disease [90, 91]. However, even if the percentage of patients who may benefit from resection is probably small, the majority of authors agree that the local treatment of hepatic metastases, compared to palliation or systemic treatment, significantly improved overall survival among these patients [56]. In particular, overall 5-year survival rate of gastric cancer metastatic to the liver ranges between 0 and 10% [58, 59, 92], whereas it rises up to 20% after curative hepatectomy in the literature [64–68, 73, 93]. Furthermore, taking into consideration the only article about hepatic

metastasis local re-treatment after recurrence, the authors found a survival advantage in local treatment repetition [94].

In the current literature, many factors resulted in influencing the survival rate of gastric cancer patients with hepatic metastases. In particular, the prognosis seems to be significantly worsened by greater extent of hepatic involvement (H3) or macroscopic peritoneal dissemination (P1) detected at surgical exploration, by greater number (>1) and size of hepatic metastases in H1-2 and P0 patients [61, 62, 95, 96], by greater tumor size (T4), nodal involvement (N+ independently by the extension of the metastatic spread) or higher grading (G3) [63, 80, 97], and the timing of liver metastases diagnosis if metachronous to the primary tumor diagnosis [68, 70, 91]. Therefore, these factors should be considered as possible confounding factors in the future studies. In addition, considering all these prognostic factors, some authors suggested the necessity to clearly identify the patients which could benefit from surgical treatment, in order to offer a chance to cure the patients who have good prognostic factors and to avoid overtreatment in case of absence of these factors [56].

Taking into account local procedures for hepatic metastases, no consensus about standardized therapeutic regimen for metastatic gastric cancer has been achieved yet, so that a variety of alternative, multidisciplinary therapies have been recommended by clinical practice guidelines, including radiofrequency ablation (RFA) [86], transarterial chemoembolization (TACE) [98], microwave coagulation therapy (MCT) [95], adjuvant chemotherapy, molecular targeted therapy, or palliative supportive care [99–101]. In particular, RFA, MCT, and TACE could additionally be used in the case of an isolated metastasis in either half of the liver, in the absence of extrahepatic disease [102, 103]. For example, in some series of patients treated by RFA, survival rates resulted similar to those reported in the best surgical series [61, 104, 105].

In summary, if indications are appropriate, surgical approach in the case of hepatic metastases from gastric cancer should always be undertaken, after a multidisciplinary discussion, a proper patient selection, and the exclusion of additional secondary tumors or extrahepatic metastases. Neoadjuvant chemotherapy, as well as other multidisciplinary, adjuvant treatment modalities, may have a synergic role if combined with surgery. And in particular, local interventional procedures, such as RFA, MCT, or TACE, may be useful in selected patients.

4. Liver Metastases from Breast Cancer

Breast cancer is the most prevalent cancer among the female population worldwide, with a peak of incidence after menopause. Despite the gradual reduction of locally advanced breast cancers and the consensual increase of early breast cancer – thanks to the introduction of an organized mammographic screening [106, 107] and the evident therapeutic improvement – stage IV breast cancer continues to represent a fatal disease and its incidence does not seem to reduce with the passing of years. The first explanation may be that distant metastasis in the hematogenous way does not depend on tumor size nor on lymph node involvement, which is usually an expression of metastasization in the lymphatic way. Secondly, groups of patients who more frequently present distant metastasis from breast cancer do not usually represent a screening target, such as young premenopausal women.

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Typical breast cancer metastasization sites are, in order of frequency, the bones, liver, lungs, and brain. In our institutional casistic, distant metastasis prevalence among breast cancer patients resulted about 10%, which in about the 20% cases are synchronous with the primary cancer diagnosis, whereas the remaining 80% of women developed metachronous metastasis.

In the context of the incidence of distant metastases, hepatic ones vary from 5 to 34% [108–111], with values rising up to over 60% in autopsy series [112]. The prognosis is poor in this area being the median survival of 1–20 months from the diagnosis of liver metastases [108, 109, 113, 114]. Long survivals seem to be related to a positive endocrine treatment response, performed in the subgroup of patients with positive estrogen receptor pattern, with median survivals around 14 months compared to 4 months in the other cases [114]. Overall, with current chemotherapy regimens, survivals ranging from 1 to 25 months are obtained. However, after discontinuation of chemotherapy, only 40% of cases are responsive to the same regimen.

Studies on the outcome of local treatment currently do not offer univocal results, probably because of possible selection bias of cases operated and/or treated with other modalities such as thermal ablation, destruction with yttrium, or chemoembolization. On average, in the cases undergoing liver resection, the median survival is of 27–63 months. In almost all studies, however, there is a subgroup of patients with very encouraging survival responses, and many efforts have been directed toward the identification of the related prognostic factors. At the moment, it seems that the receptor status of the primary tumor, the value of Ki-67, the number of liver lesions removed, resection margin, and menopausal status may play a positive role on prognosis [115]. However, the proportion of patients that presents the favorable characteristics is small, not exceeding 3% of patients [116].

Over the past 20 years, the survival of patients with stage IV has been gradually improving as a function of new chemotherapy regimens, local control with radiation therapy, and other forms of intervention. As previously stated, the metastatic breast cancer involves with a high frequency the bones, lungs, liver, and brain. Individually or predominantly considered within the concept of "oligometastatic state," each of these sites leads to different outcomes with median survival of 43 months for nodal involvement, 33 months for metastatic bones, 22 months for the lung, and 12 months for liver. For multiple sites of metastases or brain metastases, survival values collapse, respectively, to 9 and 3 months [117]. Given the prognostic value represented by each metastatic site, the meticulous choice of the liver resection candidate is obvious. In fact, in the studies that show the reference global population, the rate of resection is absolutely modest, around 0.3%, but with a high resection rate, 81%, being the non-resected cases due to intraoperatively carcinomatosis diagnosis [118–120].

In the most recent and representative case studies series, resection of breast cancer liver metastases shows that the appearance of metastases follows the discovery of the primary tumor of an average of 40 months (23–77), the indication for resection concerns cases with single lesion or a maximum of two lesions, with dimensions within 3 cm in most cases, and that in most cases, major resections were performed (more than 3 liver segments) with values of radical resection (negative margin resection) of more than 80% [118–125]. The average survival values reported by these series range from 32 to 74 months and the 5-year

follow-up survival rates are of 34–80%. Interestingly, the rates of postoperative mortality are of 0% and morbidity of 0–44% that make absolutely acceptable the surgical treatment in these cases thus selected. Prognostic factors evaluated in multivariate methods ultimately lead to the conclusion that the only real risk factor is represented by the positive resection margin.

Considering these results and taking into account the chemosensitivity of breast cancer emerges the consideration that even in cases of more consistent hepatic invasion, in the absence of brain and lung lesions, it can be considered a space for liver surgery [126]. It is evident from many series that survival is influenced by the state of the free margin, although not always the gap between R0 and R1 leads to a robust statistical difference [122]. Therefore, considering the possibility of a chemotherapy response and the greater possibility of surgical treatment also linked to the impact of new intraoperative technologies (e.g., radio frequency and microwave), it seems natural to expect in the immediate future an expansion of the surgical indications for breast cancer liver metastasis.

As a paradigm of these considerations, we take as example the case of a woman who after two breast surgeries for two metachronous cancers underwent chemotherapy for the appearance of liver metastases, with partial response, followed by rupture of one of the lesions and therefore emergency surgery for hemoperitoneum. Subsequently, after about six months, she developed a second hemoperitoneum treated again by surgical hemostasis. Afterward, she was transferred to our center and it was then made with palliative intent a major liver resection, left hepatectomy en bloc with part of the stomach and removal of two peritoneal implants. In the same intervention, the other two lesions on the right liver lobe were not treated. These two lesions were later treated by radiofrequency ablation combined with transcatheter arterial chemoembolization. Surprisingly the patient is alive and disease-free 43 months after the last procedure.

5. Conclusive Summary

Thanks to the improvement in the diagnostic and therapeutic pathways, the number of cancer survivors is progressively increasing, as well as the number of metastatic patients. Taking into consideration all primary solid tumors, the liver represents the most frequent site involved by distant metastasization, also due to its anatomical position and its important blood reception from the majority of digestive organs.

Despite the abundant literature and guidelines about colorectal liver metastases, there is still great debate about the treatment strategy in the case of non-colorectal ones. Anyway, many experiences have been published in the last decades about surgical treatment of the most frequent non-colorectal liver metastases. In particular, we reviewed surgical strategies in the case of hepatic secondaries from neuroendocrine tumors, gastric cancer, and breast cancer. And in every case, the literature suggests a role for hepatic surgery for patients with resectable hepatic disease.

However, the number of considered patients is often very limited as well as the statistical strength of the current literature. Therefore, further randomized controlled trials are required in order to better define the benefit of hepatic surgery in these kinds of patients.

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