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GUEST EDITORIAL

Liver surgery for noncolorectal nonneuroendocrine metastases

The place of surgery in the management of resectable liver metastases of colorectal malignancies has been recognized and well established. Moreover, cooperation between surgeons and oncologists permits shrinkage of unresectable liver metastases, making these suitable for surgical treatment. The clear distinction between resectable and unresectable metastases in this field is probably near to becoming obsolete. For symptomatic metastatic neuroendocrine tumors, hepatic resection, including liver transplantation, may offer long-term palliation in many cases and cure in some others.

In contrast, the role of hepatic surgery in patients with liver metastases from noncolorectal nonneuroendocrine (NCRNNE) carcinoma is not well defined. There are many reasons for this lack of clarity. Many reports include neuroendocrine patients in their analysis and consequently alter survival data. Indeed, most series are not comparable in terms of mid- and long-term (tumor-free) survival, as they include patients with NCRNNE hepatic metastases from different primary malignancies, different tumoral behaviour and different frequency of isolated hepatic metastases, different sensitivity to neoadjuvant or adjuvant therapy (chemotherapy or radiotherapy) and different length of delay between the diagnosis of the primary tumor and the liver metastases (synchronous or metachronous). Further, most of the studies span at least 10 years, so the role of the chemotherapy should be carefully considered, since the protocols have evolved rapidly during this time.

Due to these heterogeneous characteristics, the conclusions of many comprehensive studies are that prognostic factors for liver metastases from NCRNNE remain uncertain.

In recent years, despite the poor results, liver metastases suitable for surgery have been operated. The main reasons for this attitude include the refinements in preoperative work-up, anesthesiology management, perioperative care, and surgical technique that make liver surgery reasonably safe; decreasing operative mortality to approximately 1% in tertiary referring centres. Also, there are no data that actually suggest the usefulness of alternative treatments for NCRNNE liver metastases, so this reinforces the role of surgery.

In the absence of certain indications, the patients have been treated surgically and, as for large hepatic metastases from colorectal cancer where it is now possible, after chemotherapy, to carry out a hepatic resection resulting in long survival, a more aggressive surgical approach has been observed. Since more accurate prognostic indications are still mandatory, the aggressive policy used by some surgeons and oncologists, in relation to metastases confined to the liver, should be moderate considering generic variables, such as disease-free interval (DFI) from the primary tumor. The DFI between treatment of the primary tumor and the development of liver metastasis is viewed as a surrogate marker for tumor biology. Twelve months is considered as generic minimum period between primary tumor and secondary disease to give an indication for surgery for liver metastases. After this first year, any further time interval should be considered as a progressively increasing positive prognostic factor. A longer DFI is believed to indicate less aggressive tumor biology.

The role of liver resection for NCRNNE liver metastases is still a matter of discussion, mostly because there only small studies have been carried out in this field and the conclusive outcomes are collective and not specific for each type of tumor.

Since different primary tumor types have different underlying tumor biology, the ideal study should concentrate on only one tumor type to allow meaningful conclusions. This is why in recent years, some studies have started to analyze the NCRNNE liver metastases only in relation to the primary tumor, to improve knowledge and satisfy more questions. However, for some types of metastases the number of cases reported in a comprehensive review or separately is still small and, even if the results are encouraging, more data are necessary to have a safe indication, especially for metastases originating from primary cancer considered to have a poor prognosis.

As regards pancreatic cancer, good survival rates after an aggressive approach (including pancreatic and hepatic combined resection) have been reported. However, the small number of long-term survivors had cystoadenocarcinoma as primary tumor, and the biological behavior of this type may be different from pancreatic ductal adenocarcinoma. This aggressive approach needs validation reports and a more

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extensive number of patients. For isolated liver metastases from pancreatic cancer, liver resection might be an effective treatment for highly selected patients (i.e. single metastases, DFI >24 months), but further specific studies are necessary to better clarify the role of hepatic resection.

Liver metastasis from gastric cancer is usually considered a poor prognostic factor, but recent studies based on specific metastases from this kind of tumor began to give us some defined indication. Survival after hepatic resection for gastric cancer metastases is poor, but long-term survivors exist, so careful selection of patients is mandatory. Hepatic resection is indicated in case of solitary and metachronous metastasis and when a complete resection can be performed safely. Patients with optimum prognosis are those with a primary tumor located at the antrum, without lymphatic or venous invasion, and with a minimum DFI of 1 year.

The indication for hepatic surgery in patients with liver metastases from ovarian cancer is similar to that of patients with diffuse metastatic disease: the two most important factors affecting the recommendation for surgical resection are the ability to achieve overall optimal cytoreduction and a minimum of 1 year of DFI. Randomized studies are needed to evaluate the role of the surgery beyond chemotherapy and also whether the similarity of ovarian cancer and colorectal carcinoma suggests benefit for patients with metastatic ovarian cancer.

For liver metastases from breast cancer, surgery is indicated for patients at low risk, with liver metastases completely resectable and with no extrahepatic disease. Other positive prognostic factors are a DFI >12 months, less than four nodules and a positive hormone receptor status. Still, if good results have been achieved, surgery must be considered as a part of a multimodal approach with endocrine and chemotherapic treatment, and an objective response or a stabilization after chemotherapy is always requested before surgery. The patients are frequently referred to the surgeon after numerous courses of chemotherapy, which definitively impair liver function, exacerbating the risk of hepatectomy. That is why functional tests or decisional schemes, as used for cirrhotic patients, have been utilized to avoid postoperative liver insufficiency.

Testicular cancer metastasizing to the liver is mainly cured by chemotherapy. After chemotherapy, if metastatic lesions are still present on radiography and serum markers are normal, the patient can be submitted to surgical resection. The best results are achieved when there is no evidence of germ cell cancer in the histological specimen, reaching survival rates of 89% at 4 years without relapses of disease.

The key to achieving long survival after hepatic resection of metastases from sarcomas is an R0 resection. However, the most important independent predictor of a good outcome is a DFI from primary tumor of >2 years. In the field of sarcomas, GISTs must be distinguished because neoadjuvant/adjuvant treatment with Imatinib can allow a down-staging and an improvement of overall survival.

Patients affected by liver metastases from kidney cancer can achieve significant survival after hepatic resection, if the primary tumor is free of invasion, the DFI is >24 months, the diameter of lesion is <5 cm and a radical resection is possible.

Patients affected by liver metastases from adrenal cancer can achieve good survival after complete hepatic resection of metachronous metastases in case of a minimum DFI from the primary tumors of 12 months.

Liver metastases from lung cancer can be treated in the absence of extrahepatic disease with a minimum DFI of 12 months.

In this special issue of *HPB* focusing on surgical indication for NCRNNE liver metastases, the surgical ratio for this rapidly evolving field is addressed. This issue cannot provide a complete exposure of all types of tumors, but the most frequent are analyzed in order to better address these patients to the right treatment.

Each of the contributors discusses indications for surgery and its result on liver metastases from different primary tumors. They discuss the literature data and, where possible, their personal results. The authors of this issue have demonstrated that hepatic resections are more and more indicated and, in selected patients, the oncologic results seem to be very encouraging.

I am sincerely grateful to all the authors for their outstanding effort in contributing to this issue, and to the editor for permitting me to realize this project.

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