



Laparoscopic liver resection for non-colorectal non-neuroendocrine liver metastases: narrative review of literature

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Abstract: Liver resection for resectable colorectal and neuroendocrine liver metastases is the treatment of choice, and laparoscopic approach is considered safe and viable in these patients, with less postoperative complications compared to open surgery. Liver surgery for non-colorectal non-neuroendocrine liver metastases (NCNNLM) is a controversial issue as well as the role of minimally invasive surgery for this heterogeneous groups of malignancies. Patients with NCNNLM in fact are frequently referred to palliation due to the presence of extra-hepatic disease, and even in case of surgery, they usually undergo laparotomic approach. This article aims to examine and consider some of the most relevant contribution to this issue published in literature, trying to take stock of this still unsolved topic of oncologic surgery. Several studies have stated that liver resection can improve outcome in patients with NCNNLM, after careful selection based on different aspects and characteristics. Several criteria of selection have been identified, trying to select patients who could benefit more of surgery, and they include primary tumor histology, age, type of hepatectomy, presence of extra hepatic disease (EHD), length of disease-free interval. Recent reports not only confirm the pivotal role of selection of patient but also specify the technique of liver surgery (open *vs.* laparoscopic technique), confirming that laparoscopy has better short-term outcomes such as acceptable operative times, blood losses and conversion rate, whereas long-term survival is comparable to those of open liver resection. In conclusion, careful patient selection is the mainstay of treatment of NCNNLM, based on tumor biology and characteristics, and laparoscopic surgery seems to be an adequate approach. Unfortunately, evidence in literature remain scarce or even contradictory, lacking a sufficient number of patients for each tumor. Not rarely studies take into considerations different criteria of selection, which results in additional variability of cohort of populations among studies, and difficult in comparing them.

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Introduction

The advantages of laparoscopic liver surgery over its open counterpart are well known, for both primary liver tumors (1,2) and liver metastases of colorectal (3) and neuroendocrine origin (4), and they include less pain, better

aesthetic result, shorter hospital stay, less blood loss.

Laparoscopic liver resection (LLR) for colorectal liver metastasis (CLM) is the standard of care, with 5-year survival rates after surgery of 63% (5), which is superior to medical therapy alone, and less postoperative complications

compared to open surgery (6). LLR for neuroendocrine metastases is the treatment of choice as well, with 5-year and 10-year overall survival of 60% and 35% respectively (5).

These encouraging results cannot be transfer to NCNNLM (non-colorectal non-neuroendocrine liver metastases) because these are an heterogenous group of malignancies with different primary tumor location and characteristics e.g. biology, histology, type of metastatization.

Extra-abdominal tumors in fact reach the liver through systemic circulation, so other organs have the same probability of being involved. For this reason, most of patients with NCNNLM have also extra hepatic disease (EHD) and are usually referred to palliative care, considering stage IV disease a contraindication to surgery.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/ls-20-109>).

Methods

The authors research was conducted on PubMed database, regarding English-published literature without limitation to time or study design.

Discussion

In one of the first report in 1997, Harrison and colleagues (7) published the data of their 15-year experience in their institution concerning this issue. On multivariate analysis three characteristics were identified as predictive of better survival: short disease-free interval (less than 36 months), curative resection, and primary tumor type (genitourinary histology had better survival than soft tissue, which was greater than gastrointestinal). Harrison concluded that “hepatic resection for patients with NCNN metastasis has value in carefully selected patients”.

Subsequent studies tried to identify predictive factors of poor outcome, in order to select patients who could benefit more from surgery. On these assumptions, Adam *et al.* (8) designed a risk model of prognosis (from 0 to 10) to estimate survival of patients with NCNNLM, which has been widely validated in Western and Asian populations. The Adam score include: presence of extra-hepatic disease, type of hepatectomy, R2 resection, age of patient, length of disease-free interval between treatment of primary tumor and diagnosis of liver metastases, primary tumor histology.

Despite this progress, evidence in literature regarding

this controversial issue are still scarce, lacking a sufficient number of patients for each tumor. Not rarely studies take into considerations different criteria of selection, which results in additional variability of populations among studies and difficulty in comparing them. Moreover, reports seldom specify the technique of liver surgery (minimally invasive *vs.* laparotomic).

Metastases of gastrointestinal origin, first of all gastric and intestinal GIST, were the most representative group (39%) in the retrospective cohort examined by the recent work of Aghayan (9) followed by melanoma; in the multicenter cohort published by Wakabayashi *et al.* (10) about 205 patients with non-colorectal liver metastases treated between 2000 and 2013, the most common primary tumor was gastric cancer (39%) in line with the high prevalence of gastric tumor in Asian population; in the Adam study (8) the most representative origin was breast cancer (32%).

Recent studies found postoperative outcome of LLR for NCNNLM comparable to/or better than those achieved by OLR for same metastases (11), as well as LLR for CLM and NLM (3,4,12,13). Laparoscopic liver surgery is increasingly used also for major hepatectomies and tumors in the posterior segments. Therefore, the minimal invasive approach should be an essential component of the careful multidisciplinary selection of patient referral to surgery.

Some component of the Adam score in fact (major hepatectomy, R2 resection) are influenced by the technique of liver resection (open *vs* laparoscopic).

Parenchymal-sparing resection limits the invasiveness of surgery on the liver and the risk of consequent postoperative liver failure, facilitating potential re-resections. For CLM, it has been demonstrated that R1 resection is not associated with increased local recurrence or decreased survival and it seems that parenchymal-sparing resection could be an oncologically adequate procedure for NCNNLM as it is for the aforementioned CLM (3,13,14). In recent papers, in fact, R1 resection is associated with acceptable low recurrence in the resection bed (9).

Taking for granted the role of surgery in well selected patients with NCNNLM, recent papers move target on forward, focusing their attention on the role of laparoscopy in contrast to open surgery (15,16) confirming that laparoscopy has better short-term outcomes such as acceptable operative times, blood losses and conversion rate, whereas long-term survival is comparable to those of open liver resection. In a recent work published in 2015 (16), 24 patients (11.5% of the entire cohort) affected by NCNNLM underwent laparoscopic resection. Survival

analysis performed on this subgroup of patients documented 83.3% 3-year OS. As expected, no extra-hepatic disease, long disease-free interval, limited number of liver metastases, were related to better survival.

Further studies suggest that better results could be achieved by combining laparoscopic surgery with systemic chemotherapy and local treatment (17): studies report better outcome for metastatic GIST when imatinib therapy is associated with surgery, instead of monotherapy alone (18-20). Neuman *et al.* suggested about breast cancer that, although surgery may provide some advantages in term of survival, it is noted especially in patients with ER/PR positive and/or HER-2/neu-amplified disease (21).

The multimodal management of tumors, combining surgery with cytotoxic chemotherapy, novel molecular targeted and biological agents is a double-edge sword because can severely injure the liver (22). Liver damage caused by anticancer treatment can presents with several clinical and histological forms, ranging from liver failure and death, to mild rise in liver enzymes (23) that may postpone scheduled treatment or complicate hepatic resection with curative intent.

Systemic chemotherapy can be started earlier in case of LLR for hepatic metastases, than after open liver surgery, which might relate to better long-term outcome (24). Several series demonstrate less hepatic failure after laparoscopic surgery than after laparotomy surgery in patients affected by liver cirrhosis (25-27). We should theorize the same benefit in case of liver damage after neoadjuvant chemotherapy.

In conclusion, careful patient selection is the mainstay of treatment of NCNNLM, based on tumor biology and characteristics. In patients referred to liver resection, laparoscopic approach is safe and feasible, without compromising the oncological radicality. Nevertheless, evidence in literature are based mostly on retrospective cohort studies, thus further researches are necessary.

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