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Hilar Lymph Node Involvement in Colorectal Cancer Liver Metastases – An Overview

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Abstract

Hepatectomy is the only possible option for cure in any treatment strategy of colorectal liver metastases, and several studies have shown good results, with five-year survival rates ranging from 27 to 56%. Several clinical and pathological predictive factors for survival after liver resection have been studied and the metastatic involvement of the hepatic hilum lymph nodes indicates a poor long-term prognosis. Despite variable results, some authors have reported a not-insignificant improvement in survival rate in liver-metastasis patients with hilar-lymph-node involvement who undergo combined liver resection and lymphadenectomy. Due to the low rates of morbidity and mortality for liver-resection surgery, several specialized centers perform liver resections combined with lymphadenectomy in selected cases. It should be noted that the therapeutic value of systemic lymphadenectomy is not yet entirely understood, and only controlled studies comparing groups with and without lymphadenectomy can fully resolve the issue. In any case, hilar lymph node dissection has been shown to be a useful tool for improving the accuracy of extrahepatic disease staging, regardless of its impact on survival. The authors review the incidence and the clinical impact of hilar lymph node metastases, and analyses the possible beneficial role of systematic lymphadenectomy in patients who have undergone liver resection for colorectal-cancer metastases.

Keywords: Hepatectomy; Colorectal carcinoma; Lymphatic metastasis

Review

For patients with colorectal cancer liver metastases (CRCLM), hepatic resection remains the best treatment option, with reported 5-year survival rates of 27% to 56% [1-3]. Technical improvements and pre-operative chemotherapy has been shown to increase resecability in a substantial number of cases and allowed an expansion of indications to include patients with large and multiple or bilobar lesions [4-6] with acceptable morbidity and mortality [6,7].

Several clinical and pathological predictive factors for survival after hepatic resection have been studied. These factors include primary tumor staging (pT and pN), pre-operative level of carcinoembryonic antigen (CEA) and/or carbohydrate antigen 19.9 (CA 19.9), the interval between the diagnoses of the primary and the metastatic lesions and the presence or absence of extra-hepatic disease and lymph node involvement of the hepatic hilum. Despite some discrepancies in results, most studies have shown that lymph node involvement at the primary site (pN), synchronicity of the lesions, four or more hepatic lesions, and hilar lymph node metastases constitute the major negative prognostic factors, with significant impacts on long-term survival [8-12].

Extra-hepatic disease, especially hepatic lymph node involvement has long been regarded as an exclusion criterion for curative hepatectomy because the prognosis was considered poor, even when adequately resected [13,14]. Recently, however, studies advocate resection for patients with limited extra hepatic disease, especially lung metastases, in highly selected patients providing long-term survival with R0 resection [15-17].

The hepatic lymphatic vessels fall into three categories depending on their locations: portal (the most important), sublobar, and superficial lymphatic vessels [18]. The theoretical mechanisms of intrahepatic spread for CRCLM include metastasis from the primary tumor, but also *de novo* metastases from the pre-existing liver metastases [19,20]. It is believed that lymph node involvement in patients with CRCLM may actually constitute a tertiary metastasis or "metastasis of a metastasis", a concept proposed by August et al. [19] and subsequently reinforced by other studies [21,22].

The incidence of macroscopic lymph node involvement varies between 2 and 10% in major series [19,23,24], and they indicate a poor long-term prognosis. Based on these results, most authors have considered macroscopic lymph node involvement to be a contraindication to liver resection [12,25,26]. Studies that have employed systematic dissection of suspicious and non-suspicious hilar lymph nodes to diagnose microscopic involvement have found an incidence of 14% to 30% [13,27-29] which proves that assessments based only on palpation and macroscopic inspection are not accurate. A controversial issue is the role of lymph node dissection in major-chain sampling without a complete dissection of the hepatic hilum and the celiac trunk. Kokudo et al. [30] have shown a tendency towards 12B chain involvement in patients with metastases on the right hepatic side and towards 8A chain involvement in lesions located on the left side. Ercolani et al. [27] found that pericholedochal and common hepatic artery stations were the key stations for lymphatic spread from liver tumors, other authors, however, have not found a relationship between the chains involved and the topography of the hepatic lesions [14,23,28,29]. Elias et al. [29] diagnosed microscopic lymph node involvement in several of the lymphatic chains studied without a continuous progression from one chain to another (lymph node jumping metastasis). Therefore, any specific lymph node group

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will reflect the true state of ganglion involvement in patients with metastatic hepatic lesions and a minimum of 3-4 regional lymph nodes should be dissected to obtain a reliable statement on lymph node status [27,28,31].

The aforementioned studies used hematoxylin and eosin (H&E) stain to evaluate hilar lymph nodes harvested at the time of liver resection, which is not the most sensitive modality for detecting micrometastases. A study with hilar sampling but not routine lymphadenectomy showed the presence of micrometastases in 23% of the patients, and the presence of hilar micrometastases was associated to a shorter recurrence-free survival [32]. We have previously shown our initial results of a prospective study with hilar lymphadenectomy during hepatectomy for colorectal metastasis showing an overall frequency of hilar involvement of 23.6% with 18% of patients presenting micrometastases by H&E or immunohistochemistry analysis (IHC) [31]. Immunohistochemistry is particularly helpful in the detection of micrometastases because it associates a specific immunological reaction with the morphological control of immunoreactive cells. The association of both techniques (IHC and serial sections) as employed in our study seems to be recommended for further evaluation of H&E-negative nodes [33]. Micrometastases research has been routinely used in breast cancer and melanoma cases [14,34-36], and several studies on other malignancies have confirmed that it is able to expand diagnostic sensibility [37-39].

Fault of this lack of consensus, the real incidence of microscopic hilar involvement and/or micrometastases remains dependent of the definition criteria and the techniques employed by each author.

One of the most relevant questions is whether hepatic resection is indicated in patients with affected hilar lymph nodes. Studies that have examined the impact of microscopic lymph-node involvement on survival have found it to have a negative effect [13,14,28]. Nevertheless, some authors have reported significant survival rates in liver metastasis patients with associated hilar lymph node disease who undergo combined liver resection and lymphadenectomy [14,23,40-42]. Among these results, Kokudo et al. [30] have shown that the survival rate of patients with lymph node disease who undergo R0 resection and lymphadenectomy is significantly higher than that of residual liver disease patients without lymph node metastases who undergo liver resection (17 months versus 8 months, $p < 0.05$). Some authors therefore suggest a possible benefit from resection and hilar lymphadenectomy in patients with lymph node involvement [23,43]. Two other studies have found three-year survival rates between 38 and 45% in patients with compromised liver pedicle lymph nodes who undergo liver resection combined with lymphadenectomy [14,40]. However, the location of the compromised lymph nodes seems to be a major issue and resection of positive lymph nodes located in area 1 (hepatoduodenal ligament/retropancreatic area) may offer long-term survival benefits, on the contrary, when lymph node located in area 2 (along the common hepatic artery/celiac axis) or area 3 (para-aortic) are positive, the long-term survival is significantly worse [14,40]. Recently, Adam et al. [44] described an 18% global five-year survival rate in a selected group of patients with hepatic metastases and compromised hepatic hilar lymph nodes who underwent hepatic resection and lymphadenectomy.

Comparing the prognosis of patients with IHC or H&E-only detected micrometastases, it seems that the former may be related to a better overall survival [32], although studies in colon and breast cancer patients have not found a relationship between IHC-only metastatic disease in regional lymph nodes and tumor recurrence. [45,46]. Due to the low morbidity and mortality rates in liver-resection surgery, several specialized centers (including ours) perform liver resections combined with extended lymphadenectomy in selected cases (Figure 1).

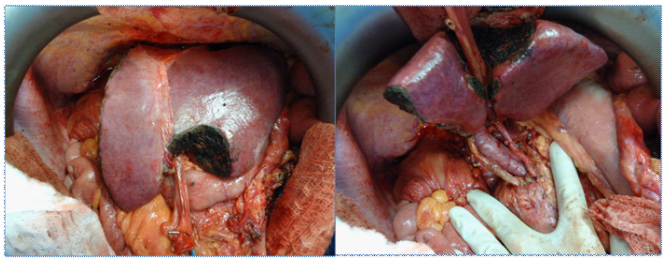

Figure 1: 57 years-old man submitted to right hepatectomy, wedge resections at segments 2 and 3, and hilar lymphadenectomy for CRCLM.

It should be emphasized that the therapeutic value of systemic lymphadenectomy is not yet entirely understood, and that only controlled studies comparing groups with and without lymphadenectomy can fully solve the issue. In any case, hilar lymph node dissection has been shown to be a useful tool for improving the accuracy of hilar nodal involvement and thus disease staging, regardless of its impact on survival, and may potentially influence post-resection chemotherapy recommendations.

The search for microscopic hepatic lymph node involvement does not detect all patients that will relapse or those that will not. Moreover it is premature to assume that the adjuvant therapy alone is able to suppress the difference in prognosis that may be related to their presence. Before advocating systemic hepatic hilar dissection, more studies are needed to establish the value of node involvement as an independent prognostic variable. Molecular biology may help us to solve this question and better understand tumor behavior. Meanwhile, the routine search for lymph node involvement should be proposed only as part of clinical trials.

From a practical perspective, the clinical importance of lymph node micrometastases for long-term survival is not known, especially in patients undergoing systemic treatment (chemotherapy). There is a shortage of studies evaluating whether detecting micrometastases allows for better staging, is indicative of a poor prognosis, or has limited prognostic value. Despite some authors having shown a correlation between the major prognostic factors and the presence of lymph node metastases [14,29], most studies have not found such associations and have reaffirmed the impossibility of determining risk subgroups for hilar lymph node involvement [28,30-32].

Finally, it is important to highlight the possible role of systemic treatment in patients with macroscopic or microscopic lymph-node disease who undergo resection and lymphadenectomy. It is presumed that modern peri-operative chemotherapy regimens can positively influence the clinical course of these patients, possibly creating a new paradigm for the treatment of colorectal liver metastases and extending the limits of liver resection, even in patients with lymph node involvement.

In conclusion, larger studies should be performed to determine the significance of unsuspected perihepatic hilar lymph node metastases, as though the potential benefit of hilar lymphadenectomy, and of changes in chemotherapy strategy by hilar lymph node status. Indeed, subject to a consensus on their definition and standardization of detection methods, it may alter the management of CRCLM treatment in the future.

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