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Review

The histopathologic report of surgically resected colorectal liver metastases: What is clinically relevant?

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ABSTRACT

Colorectal carcinoma (CRC) is one of the most common malignancies and a major cause of cancer-related death worldwide. The liver is the most frequent site of metastatic spread, so that about half of the patients with CRC have or develop liver metastases (LM) during the clinical course of the disease. Colorectal LM can potentially be cured by surgery, but most patients still experience disease progression and recurrence after the surgical treatment. Prediction of a patient's post-surgical clinical course is mainly based on clinical parameters or the histopathological features of the primary tumor, while little attention is given to the pathological characteristics of the LM. In this paper, we review the prognostic relevance of the gross and microscopic pathological features observed in surgically resected LM and propose which information should be included in the histopathological report to guide surgeons and oncologists for the subsequent therapeutic management.

1. Introduction

Colorectal carcinoma (CRC) is a major cause of cancer-related death worldwide [1]. Liver is the most frequent site of its metastatic spread. Indeed, the majority of patients have (synchronous) liver metastases (LM) at diagnosis, or they will develop (metachronous) LM during the disease's clinical course [2,3].

In recent years, surgical resection of LM has significantly improved the prognosis of patients with advanced CRC [4]; however, most patients still experience recurrence and adverse outcome after surgery [5]. Thus, the use of prognostic factors able to stratify patients for recurrence- or progression-risk could be helpful in designing tailored post-surgical treatments. Research over the years, has been mostly focused on possible clinical parameters conditioning the prognosis of patients with CRC LM [6–8], while little attention has been given to the histopathological features of LM. Indeed, in clinical practice, the histopathological report of CRC LM is generally limited to the confirmation of malignancy and the assessment of margin status [9]. However, the pathological features of LM are more closely related to the tumor biological aggressiveness, than clinical parameters are. Therefore, in our view, they could be more helpful in predicting the postsurgical clinical course of CRC.

Herein, we review the prognostic relevance of macroscopic and microscopic pathological features of LM. We propose that some of those be included routinely in the pathological report as useful information to guide surgeons and oncologists in the subsequent therapeutic management.

2. Macroscopic prognostic parameters

2.1. LM size

LM maximum diameter has been demonstrated by several studies to be prognostically informative in patients with CRC LM [6,7,10]. For this reason, it is currently included in clinical scores for prediction of recurrence-risk [6,7,10]. However, more recent studies did not confirm its prognostic significance [11,12], possibly because of the use of different cut-off values or of the exclusion of patients with preoperative chemoradiotherapy [12]. Although there is no consensus on the prognostic relevance of LM size, we suggest that the maximum diameter of each LM be included in the gross examination heading of the histopathological report. Indeed, it could be useful to determine the efficacy of preoperative chemoradiotherapy, as downsizing is expected in responders [13].

3. Microscopical prognostic parameters

3.1. Resection margin status

Resection margin status is assessed microscopically by measurement

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of the distance between the lesion and inked margin of the liver resection. Currently, there is no consensus on the definition of positive resection margin (R1). Indeed, different prognostic studies have considered the resection margin as positive when the tumor border was < 10 mm [6], ≤ 5 mm [14], or < 1 mm [15] from the surgical cutting edge, and others have used the finding of the tumor border being in contact with the inked margin [11]. Interestingly, Hayashi et al. [14] highlighted that in the case of multiple LM the R1 margin has different prognostic value depending upon the size of the nodule where it is recorded. In particular, they concluded that R1 margin status (defined as < 5 mm) is significantly and independently associated with the overall survival of patients only if present in the largest LM. In contrast, we found in a recent study that positive resection margin in at least one synchronous LM is an independent prognosticator of shorter cancer-specific survival in patients with advanced CRC [12].

However, despite the use of different definitions, microscopically positive margin (R1) has traditionally been considered as a relevant prognostic factor [13]. We suggest, therefore, that the distance in millimeters between the tumor border and the surgical margin be recorded in the pathological report for each LM.

3.2. Tumor growth pattern

Similar to that described in the primary CRC tumor [16], CRC LM can have an expanding or infiltrating growth pattern. The former refers to tumors having well-delineated edges, pushing the adjacent liver (Fig. 1A), while the latter refers to tumors spreading freely through the surrounding tissue (Fig. 1B). The infiltrative growth pattern has been reported as significantly and independently associated with shorter disease free-survival, hepatic recurrence, and overall survival in some studies [11,17–19] but not in others [12,20].

Another system classifies tumor growth into three categories, which have different angiogenic patterns: desmoplastic, pushing, and replacement [21]. In the desmoplastic pattern, the tumor and surrounding parenchyma are separated by a desmoplastic stroma [21]. In the pushing growth pattern, the tumor is separated by liver parenchyma *via* a thin rim of reticulin fibers [21]. In the replacement pattern, the tumor cells replace normal hepatocytes [21]; with this, the reticulin network of liver parenchyma is conserved in the metastasis, a distinguishing feature from the other two patterns [21]. In addition, tumors with replacement growth do not have neo-angiogenesis and they grow by using pre-existing vessels (a process termed “co-option”) [21]. Although conflicting data have been reported on the prognostic relevance of this system [22], it may have predictive value, as tumors with replacement growth are insensitive to anti-angiogenic agents [22].

We suggest that the expanding/infiltrating growth pattern be specified in the histopathological report and that the desmoplastic/pushing/replacement growth pattern be assessed in patients treated with anti-angiogenic neoadjuvant or adjuvant therapy.

3.3. Lymphatic invasion

Lymphatic vessels represent a route of metastatic spread outside the liver. Several studies have investigated the prognostic relevance of lymphatic invasion in CRC LM [11,14,22–26] and the majority have found that it is a significant predictor of shorter disease-free and overall survival.

Lymphatic invasion in CRC LM was first defined as the presence of cancer cells (detected hematoxylin and eosin stain) in a luminal structure lined by endothelial cells in the portal area [22]. However, blood and lymphatic vessels cannot be clearly distinguished by hematoxylin and eosin stain alone. It is, therefore, recommended that lymphatic invasion is assessed by using immunohistochemistry and recorded in the presence of tumor cells within the lumen of a vessel positive for podoplanin [23]. Besides, lymphatic invasion has been shown to have prognostic significance but mainly in studies using immunohistochemistry rather than hematoxylin and eosin stain alone [11,14,22–26]. Although adjuvant treatment is not currently changed according to this parameter, we suggest that lymphatic invasion assessed by immunohistochemistry be added to the histopathological report of CRC LM.

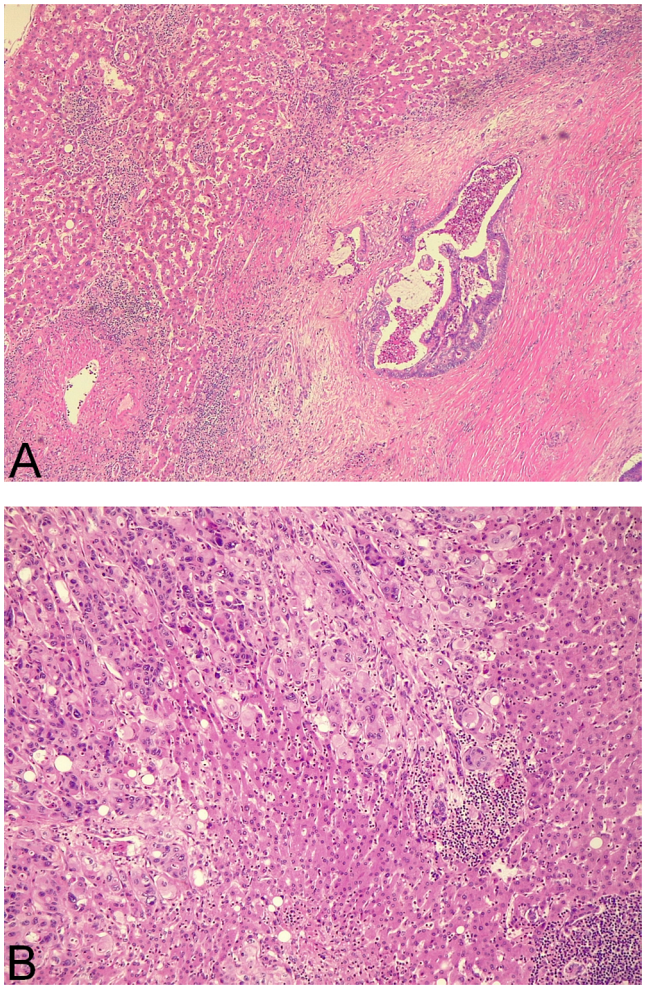

Fig. 1. (A) Colorectal carcinoma liver metastasis with expanding margin. The tumor pushes the surrounding liver parenchyma (haematoxylin and eosin stain, original magnification, ×50). (B) Colorectal carcinoma liver metastasis with infiltrating margin. The tumor freely infiltrate the surrounding liver (haematoxylin and eosin stain, original magnification, ×200).

3.4. Vascular invasion

Vascular invasion is the presence of clusters of neoplastic cells within the lumen of venous blood vessels (Fig. 2A). In LM, it can be observed in portal or hepatic veins [22]. Therefore, some prognostic studies [22,27,28], but not others [24,26,29], have distinguished between portal and hepatic vein invasion. Conflicting findings have been reported on its prognostic significance; indeed, some authors found portal and/or hepatic vein invasion to be associated with bad prognosis [9,11,14,28], while others did not observe any association between prognosis and venous invasion in LM [22,24–27]. However, given the prognostic significance in primary CRC [30] and the fact that venous invasion represents a route of metastatic spread inside and outside the liver, we suggest that it be included in the histopathological report of CRC LM and that in doubtful cases it is assessed by using immunohistochemistry against endothelial markers (*e.g.*, CD34, CD31) (Fig. 2B).

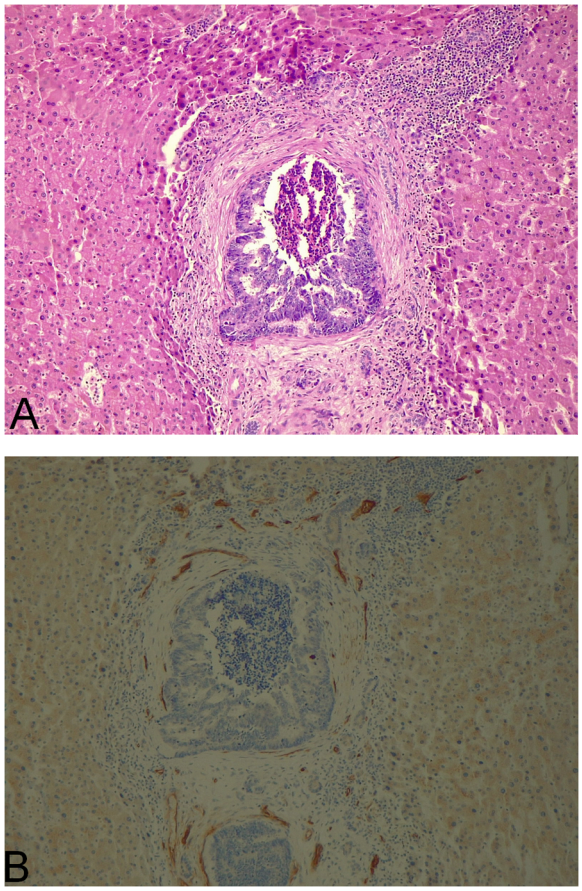

Fig. 2. (A) Venous invasion in colorectal cancer liver metastasis (haematoxylin and eosin stain, original magnification, ×200). (B) CD34 stain highlights endothelial lining confirming venous invasion (CD34 stain, original magnification, ×200).

3.5. Biliary invasion

Biliary invasion is defined as the presence of neoplastic cells within the lumen of a biliary duct [25], as detected by hematoxylin and eosin stain or immunohistochemistry against cytokeratin-7 (a marker of biliary duct epithelium) [25]. Markers of CRC (*e.g.*, CDX2) may be useful in distinguishing biliary invasion from the primitive biliary neoplasias (Fig. 3).

Stift et al. [31] found that biliary invasion is significantly associated with shorter recurrence-free and overall survival in patients with CRC LM who are receiving bevacizumab as neoadjuvant therapy. In another recent paper, Reijonen et al. [32] reported that biliary invasion was significantly associated with shorter liver recurrence-free time but not with disease-free survival and overall survival. The association with hepatic recurrence may be explained by cancer cell spread through this *via* is causing undetectable positive margins [32]. In accordance, and in our experience, cases of biliary invasion have higher probability for development of hepatic recurrence (unpublished data). However, the correlation between biliary invasion and liver recurrence has been under-studied, as the research has been focused mostly on the association with overall or disease-free survival of the patients [15,22–27]. Although an association between biliary invasion and patient survival has not been found [15,22–27], patients with postoperative biliary invasion should undergo more intensive follow up, with the aim of detecting precocious local hepatic recurrences. Therefore, in our view, the presence of biliary invasion should be added to the histopathological report of CRC LM, due to its clinical significance.

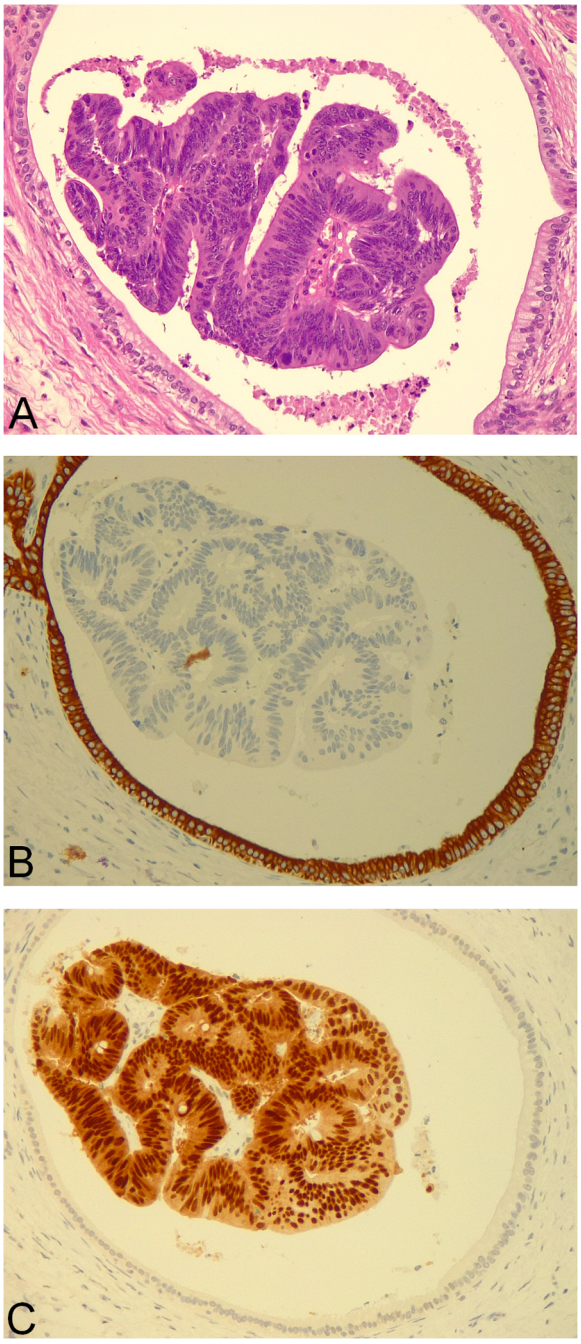

Fig. 3. (A) Biliary invasion from colorectal carcinoma (haematoxylin and eosin stain, original magnification, ×200). (B) Cytokeratin-7 positivity in the biliary epithelium and absence of staining in colorectal cancer (Cytokeratin-7, original magnification, ×200). (C) CDX2 stain in colorectal cancer within the lumen and growing in the biliary duct wall, and absence of staining in the biliary epithelium (CDX2 stain, original magnification, ×200).

3.6. Perineural invasion

The prognostic relevance of perineural invasion in LM from CRC has been evaluated in few studies only [26,28,31,33]. Perineural invasion can be assessed by using hematoxylin and eosin stain (Fig. 4) or S100 immunohistochemistry [24,26,33]. Only two studies have demonstrated its prognostic relevance in CRC LM [24,31]. In detail, Stift et al. [31] found it to be a significant but not independent prognostic factor for recurrence-free survival in patients who had undergone preoperative treatment with bevacizumab. On the other hand, Gomez et al.

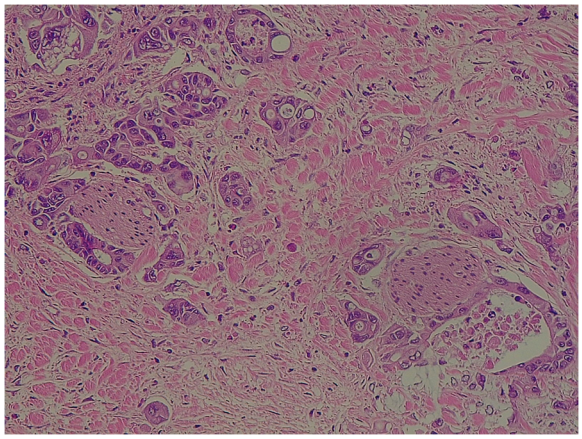

Fig. 4. Perineural invasion by colorectal cancer in a liver metastasis (haematoxylin and eosin stain, original magnification, ×200).

[24] reported its significant association with shorter overall survival in multivariate analysis.

In our view, data are still insufficient to support the prognostic value of perineural invasion in this setting. Therefore, we do not suggest including this parameter in the histopathological report of CRC LM.

3.7. Tumor pseudocapsule

Tumor pseudocapsule (Fig. 5) refers to the presence of fibrous tissue between the tumor and the surrounding liver parenchyma [11]. CRC LM may have a fibrous pseudocapsule, derived from myofibroblast collagen production consequent to compressive, necrotic or inflammatory events [34].

Several studies have demonstrated the favorable prognostic relevance of tumor pseudocapsule in CRC LM [11,26,28,34–36]. Besides, a fibrous capsule surrounding the tumor may act as a physical barrier against cancer expansion. Since only one study [20] has failed to find prognostic relevance of tumor pseudocapsule in CRC LM, we suggest that this feature be included in the histopathological report of these lesions.

3.8. Histological grading

Histological grading, assessed by the percentage of neoplastic glands according to the World Health Organization (WHO), is considered to be a relevant prognostic factor in primary CRC [37]. Studies that have evaluated WHO grading in CRC LM have not found any prognostic significance in this setting [14,22,31,38].

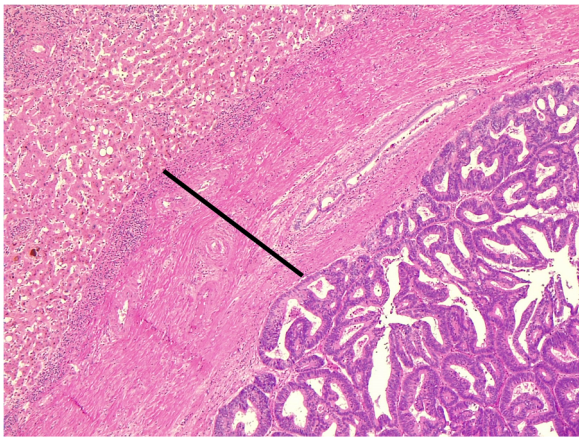

Fig. 5. Tumor pseudocapsule in a colorectal cancer liver metastasis (black line) (haematoxylin and eosin stain, original magnification, ×100).

Park et al. [29] reported that tumor dedifferentiation in CRC LM is a significant and independent prognostic factor associated with shorter recurrence-free survival. However, in their study, the authors did not apply WHO grading but rather an arbitrary grading based on the presence of solid, cribriform, spindle trabecular or palisading pattern, or single cells in more than 50% of the tumor [29].

In recent years, the prognostic relevance of a novel grading system based on the counting of clusters of at least five neoplastic cells and with no glandular formation (poorly differentiated clusters (PDC)) was demonstrated in primary CRC [39]. To the best of our knowledge, the prognostic relevance of PDC in LM of CRC has been analyzed in only two studies [11,12], which both demonstrated the correlation between PDC and poor prognosis in terms of progression-free and cancer-specific survival [11,12]. However, one of those studies used a three-tiered grading system [11], while the other considered the presence *versus* absence and the localization (in the center or periphery) of the PDC [12].

Based on the published literature, we do not recommend that WHO grading be described in the histopathological report of CRC LM. With regards to PDC grading, further studies are warranted–to assess its prognostic significance in this setting and to establish whether a three-tiered system or just their presence should be reported–before its inclusion in routine practice.

3.9. Tumor budding

Tumor budding is the presence of single neoplastic cells or clusters of less than 5 neoplastic cells at the invasive front of CRC [40]. It is a relevant prognostic factor and its routine assessment is recommended in primary CRC [40]. To the best of our knowledge, only two studies have analyzed its prognostic relevance in CRC LM [11,29]. None of them, however, have assessed tumor budding as suggested by international guidelines [40]. In one study tumor budding had no prognostic relevance [29], while in the other it was a significant but not independent prognostic factor associated with shorter recurrence-free and overall survival. Thus, data are still insufficient to support prognostic value of tumor budding in this setting and we do not currently suggest its inclusion in the histopathological report of CRC LM.

3.10. Pathological response to neo-adjuvant therapy

Patients with CRC LM are candidates for surgery if they meet criteria related to size, number, and location. In the other cases, they are initially submitted to neoadjuvant chemotherapy and sent to surgery if downsizing is achieved [13]. Several chemotherapy regimens, including FOLFOX, FOLFIRI, bevacizumab or cetuximab, can be applied as neoadjuvant treatments for CRC LM [41–43]; they also allow downsizing and for the surgery of tumors which were initially considered to be unresectable [13].

Response to neoadjuvant treatments can be assessed macroscopically by the measurement of tumor size, and microscopically (pathological response) by evaluating the presence of viable tumor cells. Pathological response has been shown to correlate with prognosis [44].

Different methods have been proposed to evaluate microscopic tumor response to chemotherapy. The first and simplest is based upon the presence or absence of residual tumor cells, so that complete pathological response corresponds to the absence of tumor cells and absence of response to any presence of neoplastic cells [44].

Another system takes into account the percentage of residual tumor in relation to the tumor area, with complete response defined as absence of tumor cells, minor response as $< 50\%$ tumor cells, and absence of response as $\geq 50\%$ tumor cells [45]. Although it also correlates to prognosis [45], in our view estimation of the tumor area prior to chemotherapy may be difficult and subjective. Rubbia-Brandt et al. [46]

developed a five-tiered tumor regression grade based on the amount of fibrosis over the percentage of residual tumor cells, so that grade 1 corresponds to the absence of tumor cells and large amount of fibrosis, and grade 5 to the absence of regression. These authors also showed that this tumor regression grade was correlated to disease-free survival [46]. Acellular mucin pools may be observed as a histopathological treatment effect in CRC LM; Fernandez-Acenero et al. [33] found that their presence is significantly associated with longer overall survival, independent from regression grade [33].

A major persisting issue relates to the assessment of pathological response in patients with multiple colorectal LM [47]; indeed, some nodules may show tumor regression and others may not [47]. Use of the mean pathological response of all metastatic nodules has been proposed for those cases [46].

In spite of the lack of a uniformly accepted method for its assessment, pathological response to neoadjuvant therapy is a relevant prognostic factor in patients with CRC LM. Therefore, it should be included routinely in the histopathological report. We also suggest reporting the eventual presence of acellullar mucin pools. For precise assessment of pathological response, CRC LM should be extensively sampled, and in cases of complete response, they should be entirely submitted to histopathological examination [46].

4. Conclusion

Tissue obtained from the surgical resection of CRC LM can give important prognostic information, which could be useful for the subsequent therapeutic management. Based on the data currently available, we suggest that the histopathological report not be limited to the confirmation of malignant disease but to also include margin resection status and distance in millimeters between the tumor and resection edge, tumor growth pattern, lymphatic, venous and biliary invasion, presence or absence of a fibrous pseudocapsule and, eventually, pathological tumor response to neoadjuvant chemotherapy. Further studies are warranted to clarify whether histological grading, PDC presence, perineural invasion, and tumor budding could actually be prognostically informative in this setting.

Declaration of competing interest

No potential conflict of interest. No financial support.

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