Journal of Gastrointestinal Surgery (2019) 23:1285–1286
https://doi.org/10.1007/s11605-019-04192-2

LETTER TO THE EDITOR

# Response to: "Liver Resection and Role of Extended Cytology and Histology"

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Received: 19 February 2019 / Accepted: 26 February 2019 / Published online: 18 March 2019


Dear Editor,

We thank Dr. Thiyagarajan et al. for their valuable comments to our study. The aim of our survey was exactly to open a debate about R1 resection for colorectal liver metastases (CLM). The extension of surgical indications to patients with major tumor burden made R1 resection a quite common event, due to disease presentation rather than to technical errors. As clearly demonstrated by our study,[1] this feeling is widely shared among surgeons and many issues about R1 surgery require further investigations. The letter by Thiyagarajan et al. raised additional interesting points.

First, as highlighted by the colleagues, 3D vision of the tumor is crucial to plan the most adequate resection with negative surgical margins, especially if CLM are close to major intrahepatic vessels. In modern liver surgery, traditional two-dimensional surgical planning based on axial imaging can be misleading. Parenchyma-sparing approach is more and more common. It improves postoperative outcome,[2,3] but increases complexity of surgery, scheduling non-linear resection planes. Similar difficulties may occur during mini-invasive surgery, where palpation is lacking. A systematic adoption of intraoperative ultrasonography (IOUS) guidance is the only way to guarantee the oncological adequacy of any resection, preventing unexpected tumor exposure.[2,4] Recently, our group even reported the possibility to detach CLM from intrahepatic vessels or to perform partial venous resection and reconstruction in case of marginal vascular infiltration by the CLM, further increasing technical complexity of resection.[5,6] The IOUS guidance was the key to perform a proper procedure, exposing the tumor only in the area in contact with vessels avoiding any exposure along the parenchyma, i.e., an R1 vascular resection that is oncologically equivalent to R0 resection.[5]

Second, the impact of dissection tools on surgical margin is still unclear. Every transection technique removes some millimeters of liver parenchyma, leading to an underestimation of the margin width at final pathology. The width of this "removed" margin is more relevant when ultrasonic dissectors are used. Does this extended removal of parenchyma allow to expose the tumor without any consequence? According to the available data, this is not the case. Even in centers systematically using ultrasonic dissectors, R1 resection is associated with higher local recurrence risk and lower survival in comparison with R0 resection. In our survey, if CLM are exposed during transection, less than 10% of the surgeons believe that the margin is removed during transection and do not perform any additional procedure.[1]

Third, Thiyagarajan et al. proposed an "extended" cytological and even histologic analysis of the resection area in order to achieve a more accurate evaluation of the surgical margin. The suggestion is of interest and needs for prospective studies, but some doubts can be advanced. Even if most surgeons retreat the resection area in case of tumor exposure (coagulation/re-resection),[1] these procedures did not show any beneficial impact on prognosis.[7] Further, pathology peculiarities of CLM should be kept in mind. CLM can be scheduled for limited resections because they do not have diffusion along portal branches as HCC do,[8,9] but have micrometastases, including microscopic vascular invasion in approximately 40% of cases and satellite nodules in about 20%, essentially in the close peritumoral area (within 2–4 mm).[10–12] Micrometastases could be accountable for local recurrence and their prevalence may explain the non-constant recurrence in case of inadequate surgical margin. Imprint cytology would detect tumor cells along the resection area, but would fail to identify deep micrometastases.

We believe that surgeons should change their mind about surgical margin, moving toward a precision medicine based on tumor biology rather than considering just morphology and

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fixed numeric cutoffs. It is still a long way to go, but some preliminary data are available. Andreou et al. reported that R1 resection loses its negative prognostic impact in patients responder to preoperative chemotherapy.[13] In our survey, three-fourth of surgeons agree with this suggestion. It is a strong basis for surgery in borderline resectable patients (high-risk for R1 resection) if responders to chemotherapy. Margonis et al. hypothesized the need for a different margin width according to the KRAS mutation status,[14] but data are still controversial. Additional parameters could be explored. The tumor growth pattern of CLM (desmoplastic, pushing, and replacement) has been associated with prognosis,[15] and could be reasonably associated with local recurrence risk. Similar considerations concern peritumoral immune infiltrate.[16,17] The liver-tumor interface is not just the surgical margin. The liver-tumor interface has a crucial role in disease progression and could open new perspectives in tumor biology assessment and therapeutic target identification.

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