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Comment on 'Histopathologic evaluation of liver metastases from colorectal cancer in patients treated with FOLFOXIRI plus bevacizumab'

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Sir,

We read with interest the article by Loupakis *et al* (2013) entitled 'Histopathologic evaluation of liver metastases from colorectal cancer in patients treated with FOLFOXIRI plus bevacizumab' published in the June 2013 issue of the *British Journal of Cancer*. This paper clearly underlines the positive impact of FOLFOXIRI plus bevacizumab, on the extent of both tumour regression and necrosis, in resected liver metastases from colorectal cancer (CRC). The authors conclude that the addition of bevacizumab leads to a high 'histopathologic activity' as compared

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to FOLFOXIRI or XELOXIRI alone. These data are important as pathologic response is considered as a new outcome end point by some authors, representing a prognostic parameter and a marker of sensitivity to preoperative treatments (Rubbia-Brandt *et al*, 2007; Blazer *et al*, 2008). Indeed, the higher the histopathologic response, the longer the survival (Rubbia-Brandt *et al*, 2007; Blazer *et al*, 2008). In this setting, we would like to mention several points that may be clinically relevant. First of all, pathologic complete response (pCR) was defined, in the study by Loupakis *et al* (2013), as the absence of tumour cells replaced by fibrosis and/or necrosis. This pCR definition corresponds to the grade 0 of the classification proposed by Blazer *et al* (2008), which is based exclusively on the percentage of residual tumour cells whatever the type of regression. However, in the Tumour Regression Grade (TRG) classification as proposed by Rubbia-Brandt *et al* (2007), fibrosis, but not necrosis, is considered as a characteristic feature of cellular response. According to these authors, the necrosis seen in CRC liver metastases is linked to spontaneous evolution of the tumour, involving insufficient vascular supply, and not to the treatment itself, thus excluding this characteristic from the TRG. In contrast, Li Chang *et al* (2012) recently showed a particular type of necrosis, so-called 'infarct-like necrosis' (ILN), characterised by large confluent areas of eosinophilic cytoplasmic remnants, located centrally within a lesion and surrounded by a rim of fibrosis with foamy macrophages (Li Chang *et al*, 2012). This necrosis is morphologically different from the so-called 'dirty necrosis', usually seen in CRC, containing nuclear debris in a patchy distribution. In this study, ILN was only seen in preoperatively treated CRC liver metastases and never observed in untreated patients who underwent primary resection of CRC liver metastases. In addition, Li Chang *et al* (2012) also noticed that ILN was significantly associated with chemotherapy plus bevacizumab treatment, although this feature was not specific and was also encountered with chemotherapy alone. Moreover, progression-free survival and overall survival were longer in patients with CRC whose liver metastases showed ILN as compared with CRC patients whose metastases lacked this feature. Besides the well-designed work by Loupakis *et al* (2013), several studies concerning preoperative treatment of liver metastases have already reported a higher percentage of necrotic areas in tumours treated with bevacizumab (Klinger *et al*, 2010; Wicherts *et al*, 2011). However, the precise type of necrosis involved in tumour response was not reported.

Our team recently confirmed the previous findings of Li Chang *et al* (2012), but on a larger population of bevacizumab-treated patients and in the setting of first-line metastatic treatment. We retrospectively reviewed archival liver CRC metastases from 91 patients who underwent secondary resection after preoperative treatment. On the basis of tumour availability, three group of patients with liver metastases were identified: a control group of chemonaive metastases ($n=29$), a group with metastases treated with chemotherapy (CT) alone ($n=31$) and a group with metastases treated with CT and bevacizumab ($n=31$). The frequency of ILN was statistically different among the three groups ($P<0.001$, Table 1). Infarct-like necrosis was observed in 53% of liver metastases of treated patients (CT only and CT + bevacizumab), but never in those of untreated patients ($P<0.001$). Moreover, the rate of ILN lesions was much higher in the CT plus bevacizumab group than in the CT group (68% *vs* 39%, $P=0.02$). The histologic features observed in our series of ILN cases were similar to those described in the study by Li Chang *et al* (2012) (Figure 1). Taken together, these data indicate that ILN is a particular feature of tumour response induced by the preoperative treatment. Therefore, it would be interesting, in the study by Loupakis *et al* (2013), to determine which type of necrosis is present in the liver metastases of the control arm (i.e., without any preoperative treatment) and to confirm that ILN might be a 'bevacizumab-related effect'.

Table 1. Frequency of ILN in liver metastases from colorectal cancer according to treatment

	No treatment, $N=29$	CT only, $N=31$	CT + Beva, $N=31$	P-value[a]
Presence of ILN	0 (0%)	12 (39%)	21 (68%)	$P<0.001$
Lack of ILN	29 (100%)	19 (61%)	10 (32%)	

Abbreviations: Beva = bevacizumab; CT = chemotherapy; ILN = infract-like necrosis.
[a] χ^2-test.

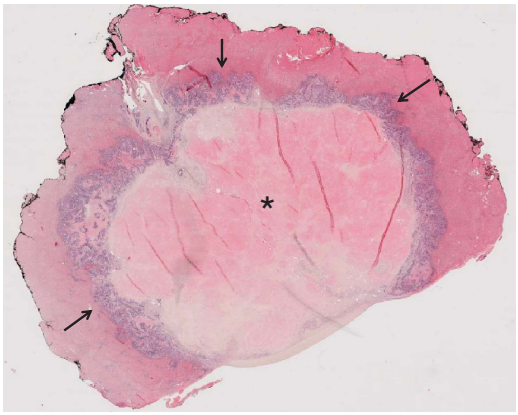

Figure 1. Subcapsular liver metastasis resected after preoperative treatment combining chemotherapy and bevacizumab. Typical well-limited lesion with central infarct-like necrosis (*), surrounded by fibrosis and residual tumour (arrows).

Finally, we would like to point out the correlation established between the histologic features and the radiologic patterns of CRC liver metastases after preoperative treatment, and skilfully discussed by Loupakis *et al* (2013). Indeed, size criteria do not seem to be accurate enough to properly evaluate the radiologic impact of treatment combining chemotherapy and bevacizumab, and morphologic characteristics are thought to be more useful parameters (Chun *et al*, 2009). In this setting, Maru *et al* (2010) suggested measuring the tumour thickness at the tumour–normal liver interface as a novel pathologic indicator of chemotherapy response in liver CRC metastases. They found that tumour thickness correlated better with radiologic response, according to morphologic characteristics than by RECIST criteria. Tumour thickness also correlated with pathologic response assessed according to the Blazer classification. In addition, greater thickness predicted shorter recurrence-free survival and this parameter remained statistically significant in multivariate analysis. Interestingly, tumour thickness was significantly smaller in patients treated with bevacizumab than in patients who were not.

In conclusion, this promising work by Loupakis *et al* (2013) highlights the impact of intensive preoperative treatments on the pathologic response of CRC liver metastases. Moreover, it equally strengthens the need for more precise and rational classification of this response, especially with anti-angiogenic therapies. Indeed, identifying ILN may represent an important contribution from pathologists when assessing chemotherapy and targeted treatment response in both clinical and research settings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Reply: Comment on 'Histopathologic evaluation of liver metastases from colorectal cancer patients treated with FOLFOXIRI plus bevacizumab'

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Sir,

We would like to thank Bibeau *et al* (2013) for their constructive comment on our article. We acknowledge that the question raised is of crucial interest and, as the evaluation of infarct-like necrosis (ILN) was not planned in our analyses, we went back to our samples in order to investigate it.

We adopted the definition of ILN previously proposed (Chang *et al*, 2012) and we found 24 (37%) out of 65 patients showing ILN, characterised by large confluent areas of eosinophilic cytoplasmic remnants, located centrally within a lesion and surrounded by a rim of fibrosis with foamy macrophages (Figure 1). Infarct-like necrosis was observed in 1 (5%) out of 28 patients in the control

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