

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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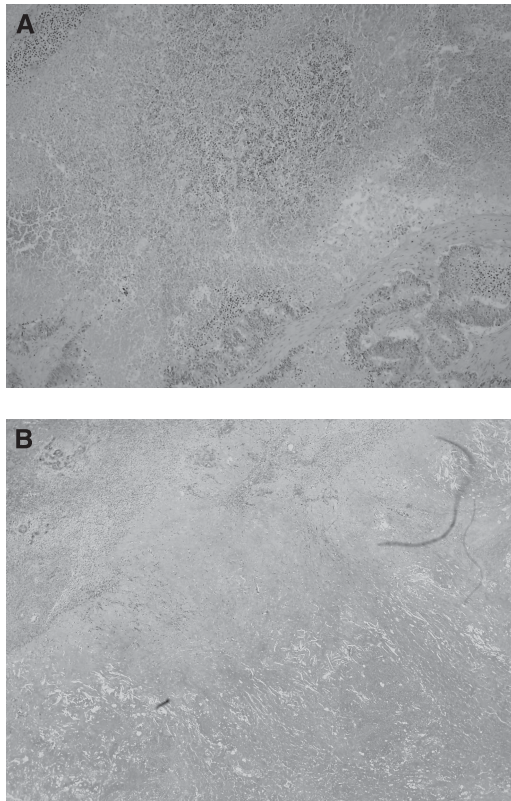


Figure 1. Examples of usual necrosis (A) and infarct-like necrosis (B).

group, in 4 (27%) out of 18 in the chemotherapy group and in 19 (83%) out of 24 in the bevacizumab group ($P < 0.0001$). The 'bevacizumab-related effect' previously described was also confirmed in our study (bevacizumab group vs chemotherapy group, $P = 0.0009$; Table 1).

In our samples, patients showing a pathologic response according to the classification proposed by Blazer *et al* (2008) were more likely to present ILN in comparison to patients showing no pathologic response: ILN was present in 71% of patients showing tumour regression grade (TRG) 1-2-3 vs 29% of patients with TRG 4-5 ($P = 0.0008$). These data strengthen the observation that ILN should be regarded as a particular feature of pathologic response induced by preoperative treatments.

Exploratory outcome analyses showed no differences in terms of progression-free survival according to the presence of ILN both among all treated patients (HR = 0.59, 95% CI:0.25-1.36; $P = 0.21$)

Table 1. Frequency of infarct-like necrosis in colorectal liver metastases according to treatment

	Bevacizumab group, N = 24	Chemotherapy group, N = 18
Presence of ILN	19 (83%) ^a	4 (27%) ^b
Lack of ILN	4 (17%) ^a	11 (73%) ^b

Abbreviation: ILN = infarct-like necrosis.
^aOne patient not evaluable.
^bThree patients not evaluable; $P = 0.0009$.

and in the bevacizumab group (HR = 0.42, 95% CI:0.06-1.77; $P = 0.19$). Nevertheless, such analyses in our cohort are affected by the relatively small sample size.

In conclusion, we definitely agree with the proposal from Bibeau *et al* (2013) to include the evaluation of ILN in future studies assessing pathologic response of colorectal liver metastases to preoperative treatments.

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