Editorial

Predicting prognosis in colorectal liver metastases

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Liver surgeons treating colorectal liver metastases (CRLM) are on the verge of fascinating times. On one hand, there is a trend towards minimally invasive, or percutaneous, approaches of liver treatment, whereas on the other hand reports on maximally invasive surgery have come out that claim survival benefit for CRLM patients if treated aggressively. In order to choose between these different treatment philosophies, the surgeon, and equally importantly the patient, need tools. Tools that will tell whether the proposed treatment option will indeed be of benefit for the patient sitting in clinic in front of you.

Brudvik and colleagues have proposed such a tool in their Annals of Surgery paper earlier this year (1). For years and years, the best prognostic tool for CRLM patients was the landmark Fong clinical risk score (CRS), published in 1999 (2), based on patient data in the era prior to that. Albeit easy to use and reasonably well-validated, the score uses only clinically available data that do not, or only to a little extent, reflect the tumour biology. And it is this tumour biology that likely dictates patient outcome. The modified CRS (m-CRS) proposed, replaces clinical factors disease free interval, number of tumours and carcino-embryonic antigen (CEA) level by the RAS mutational status of the liver metastasis. Doing so, the m-CRS is simplified, and more importantly outperforms the existing CRS. We are now able to inform our patients better, may use it for adjuvant treatment and perhaps we may adjust follow-up schemes based on risk of recurrence, although the latter two potential consequences have to be toned down as no benefit of adjuvant chemotherapy (3) nor intensive follow-up scheme (4) have ever been demonstrated.

But back to clinic now. Brudvik *et al.* have to be applauded for putting the findings of their research in the right context, and I cite: "*Prognostic scores were never designed to make decisions for eligibility or resection—even in prognostically poor groups, long-term survivors are not uncommon*" (1). For liver surgeons, a high risk of recurrence would not preclude a surgical approach to a patient fit enough to undergo the surgery, by lack of alternatives. Luckily, surgery has become a safe procedure in CRLM patients by adequate training of surgeons and concentration of procedures to high-volume centres (5). The recently presented OSLO-COMET trial (6) has taken a next step in this trend. In this randomized study it was proven that a minimally invasive laparoscopic approach to CRLM is oncologically equal to the open procedure, but has less implication on morbidity, hospital stay and quality of life. So far so good. But other trends in liver surgery go exactly the other way: technical boundaries are overcome as to increase the pool of patients qualifying for surgery. The recently published Ligro trial (7) is one exponent of this trend, showing that associating liver partition and portal vein ligation (ALPPS) can provide higher overall resection rates than the more traditional two stage hepatectomy. A further step ahead is to take the entire liver out and replace it with a donor organ. Promising results have been published (8) and working along this line, virtually no technical restrictions are left. But at a cost. The morbidity of both ALPPS and two stage hepatectomy in the Ligro trail was extremely high, not to speak about the inherent morbidity of undergoing a liver transplant. And there is where prognostication comes in. What is acceptable morbidity is dependent on the presumed benefit. If the odds of early tumour recurrence, or even death of disease, is high; a minimally

invasive approach to CRLM may be perfectly acceptable. A high-risk procedure certainly is not. But this prognostic information, based as much as possible on biological markers, needs to be available in pre-operative clinic. Intriguing results of the potential of radiomics as a predictor of survival have been published in patients undergoing chemotherapy for unresectable liver metastases (9). Treatment adjustments can be made while patients are on therapy at an early stage. But we cannot stop surgery half way. In surgery, we miss the delta, the difference in status between time point A and point B. But the potential for radiomics, based on this study, is evident.

Incorporating RAS status, or the equally promising histopathological growth pattern (HGP) (10) in real-time treatment decisions still rely on tumour biopsies. RAS luckily has a high concordance with the primary tumour (11) but it remains a proxy of the actual mutational status of the metastasized disease that is the aim of the proposed treatment. Preferentially, the metastatic mutational status is assessed, and promising results of liquid biopsies have been published in the setting of heavily pre-treated stage 4 colorectal cancer (12). Given the impact of new treatment strategies in resectable CRLM, these liquid biopsies can provide useful pre-operative information for risk stratification. And is a percutaneous biopsy, long regarded obsolete for lack of clinical implications and risk for tumour seeding, ready for a come-back?

Today, optimal information of a patient requires optimal prognostic information. Incorporation of biological information such as is been done in the m-CRS is beyond any doubt important. Translation to pre-operative risk stratification is however crucial in the coming years: stratification that will lead to maximally invasive surgery in patients unlikely to recur, but humble surgical attitude in others. One cannot beat biology surgically.

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Footnote

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