Surrogate Markers of Overall Survival in Metastatic Colorectal Cancer: An Evolving Challenge Still More Complex with Repeat Surgery.

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The gold standard endpoint for assessing efficacy of treatment in any cancer is overall survival (OS), but OS requires prolonged follow-up. Accordingly, efforts have been repeatedly made since the last decade to propose surrogate markers of OS sufficiently robust to be able to shorten the follow up duration of clinical trials. DFS at 3 years has been probably one of the most popular in colorectal cancer (1) and even more recently in gastric cancer (2) . As well PFS has been proposed with some success in renal cancer (3) but with inconsistent results in advanced gastric cancer (4). These surrogate markers are however unadapted for strategies involving surgery – particularly repeat surgery - since surgery is the only treatment able to change the condition of a patient with a tumor in place, thus with disease, to that of a patient without any tumor and therefore disease-free. Accordingly, the traditional evaluation of cancer treatments making that, when a recurrence event occurs in the history of the disease, the patient is definitively censored from the curve of disease or recurrence-free survival, should be revisited in case of repeat surgery since the patient could re-become disease-free.

In this paper, Oba et al have treated this important issue. In a study involving 371 patients with liver-limited metastases operated in a very experienced center over a 17-year period,

they confirm the survival discrepancy between Recurrence Free Survival (RFS) and OS in patients with resectable CLM and propose a new composite endpoint, Time to Surgical Failure (TSF), which seems to be more strongly associated with OS and better capable to reflect the long-term outcome. This is not surprising since conversely to RFS or DFS, this new marker integrates the survival benefit provided by repeat hepatectomy and we know that despite the tremendous progress made by chemotherapy in recent years, surgery is still the only one able to provide the best survival benefit at long term and sometimes to give a chance of cure.

One may argue that this concerns a low proportion of patients - only 10-20% are initially resectable- and for those who will further be selected for repeat hepatectomy the proportion will further reduce. However, the increasing use of the Onco-Surge strategy which combines optimal chemotherapy to downsize initially unresectable metastases, with secondary surgery, is offering more and more patients the possibility to be resected and to benefit from a prolonged survival (around 33% at 5 years – www.livermetsurvey.org). In connection, with this, when a recurrence occurs – a frequent event concerning 70-75% of patients in the study- repeat resection is increasingly proposed by most surgical teams owing to the equivalent gain in survival compared to the first hepatectomy. One of the strengths of the study is to show that this repeat surgery is not anecdotal and that repeat resections were performed in 54.3% of first relapses, 40.7% of second relapses, and 47.1% of third relapses. If traditional « primary » DFS was used, 40 to 54% of patients would have been underevaluated in terms of long term outcome since censored from the « primary » DFS curve, while they became again disease-free after the second hepatectomy. And the same will occur for further repeat resections…

One of the limitations of the study could be paradoxically the high expertise in liver surgery of the authors, making that the high proportion of repeat hepatectomy reported in the paper could not be shared by all surgical teams worldwide.

Another issue concerns the absence of any perioperative chemotherapy in the strategy proposed by the authors. Although the attitude of surgery upfront in single metachronous metastases is defendable (5), the use of neoadjuvant chemotherapy is generally supported by a randomized trial at least in terms of 3-year DFS… (6) A validation of the reliability of the TSF in this population would be useful.

A last point concerns the potential advantage of using TSF in place of OS in clinical trials. One of the advantage of a surrogate marker, in addition to its good correlation with OS, is the earlier information that it gives with regards to further OS. No evaluation has been made in the paper regarding this point but no doubt that the authors will explore soon this aspect.

In summary, we still need valuable surrogate markers of OS especially in patients submitted to a surgical or a onco-surgical strategy. With the increased expertise in hepatic surgery these patients become more and more frequent, either upfront or after conversion chemotherapy. The merit of the paper of Oba et al is to propose a new surrogate marker of OS better than DFS in resectable patients treated upfront by surgery. This marker needs now to be validated in resectable or unresectable patients receiving perioperative chemotherapy. The more the repeat surgery will be used, the less valid will be the traditional surrogacy of DFS or RFS with regards to OS.

This also extends to the largest need of harmonization between evaluation criteria regarding the effects of chemotherapy – usually the median survival from the diagnosis of metastases – and those of surgery – usually median or 5-year survival from the time of resection -. As resection may occur several months after the initiation of chemotherapy, surgically-treated patients have a reported survival (from the time of resection) underestimated with regards to the diagnosis of the disease and to the results of chemotherapy alone. To harmonize the evaluation, one may propose that results after surgery may consider both the survival after diagnosis and that after the surgical treatment. By this way, median survival from the

diagnosis could the common tool to be used either for patients exclusively treated by chemotherapy, by surgery or by the combination of chemotherapy and surgery.

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