

Surgery for liver metastasis from gastric cancer

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Surgical management of hepatic metastases from gastric cancer is becoming one of the hot topics in gastric oncology. This is matter of satisfaction for the Italian Research Group on Gastric Cancer, who actively explored this particular subject. On the basis of our data and those from the literature, in a recent editorial we sponsored a “μετάνοια” (change of mind) that could lead to include surgery among the therapeutic options for a subgroup of metastatic gastric cancer patients (1).

We note that review articles follow each other with increasing frequency and almost parallel the number of research article but, fortunately, we also observe that the number of cases begins to rise. In fact, in 2010 Kerkar and colleagues (2) reviewed 436 patients collected from 19 surgical series published over a 20-year time-span, in 2014 Fitzgerald and colleagues (3) collected 481 cases published in the period 1990 to 2013, but the last review and meta-analysis, published on line in the spring of 2016 (4), considered 991 patients who underwent liver resection for hepatic metastases from gastric cancer, recruited from 1990 to 2015. It really seems that seeds planted by a handful of Pioneers begin to grow and surgery, at least in referring centres, begins to be considered as one of the possible therapeutic options for these patients. Furthermore, the fact that a group of preminent scientists and surgeons dedicates to this topic a full meta-analysis suggests that the route we explored may be correct.

The work by Markar and colleagues we were asked to comment shows some points of unequivocal agreement among the different authors that published in this domain, resumed as follows:

(I) Surgical indications are well established: liver only

metastatic disease, preservation of postoperative liver function and surgical resection aimed to full control of hepatic and gastric disease (R0);

- (II) In the above conditions surgery suffers very low mortality (median 0%, range, 0–30%) and morbidity rates typical of all major surgical procedures (median 24%, range, 0–48%);
- (III) Pooled 1-, 3-, and 5-year survival were 68%, 31% and 27%, respectively, with a median survival of 21 months (range, 9–52 months);
- (IV) Eastern patients display better survival performances than their Western counterparts: at the considered time-point survival was 79% vs. 59%, 34% vs. 24.5% and 27.3% vs. 16.5%. Furthermore, the meta-analysis performed on comparative studies showed that:
 - (i) Surgical resection of hepatic metastases is associated to improved survival if compared to no surgical resection (HR =0.50; 95% CI: 0.41–0.61; P<0.001);
 - (ii) Patients with solitary hepatic metastasis have better 5-year survival than those affected by multiple metastases who were operated on (OR =0.31; 95% CI: 0.13–0.76; P=0.011);
 - (iii) There is no difference in 5-year survival after resection of synchronous and metachronous metastases (OR =1.28; 95% CI: 0.46–3.57, P=0.631).

In extreme synthesis, the meta-analysis we are commenting gives official approval to the clinical experiences that originated the literature on this particular topic: surgery has a role in the management of a well defined subset of

metastatic gastric cancer.

We would like to add another statement to those listed above. It is self-explaining and immediate: multi-disciplinary approach offers the best results and adjuvant chemotherapy is a major prognostic factor in this subgroup of patients (5).

To these editorialists, however, some critical points raised by the review merit special discussion.

The first and the one with greatest impact in every-day clinical practice is the selection of candidates to curative surgery. At present the curve that describes survival after surgery suffers a step drop during the first year, suggesting that some abusive procedures are performed: mortality is around 40% after 6 months and reaches 70–80% 1 year after surgery.

Some indications arise from six papers that (6-11) considered cohorts of patients as observed in every-day clinical practice and not upon super-selected populations submitted to surgical treatment.

In the different settings of the disease, synchronous and metachronous presentation, simple clinical variables may be employed to select the best candidates for curative surgery (7,8,11) and those to be excluded from hepatic resection. In the synchronous setting (7) gastric cancer $T > 2$ and scattered bilobar metastases (H3) are negative prognostic factors: median and 5-year survival was respectively 23 months and 27% for the 10% of cases which did not display the two risk factors, while patients affected by $T \geq 3$ gastric cancer and H3 metastases (30% of cases) displayed a median survival of 6 months and did not survive more than 16 months. Accordingly, in the metachronous setting (11) the variable T4, N+ and G3 showed a negative prognostic role. Patients not presenting these variables (7%) had a 5-year survival rate of 40%, those affected by two or three negative prognostic factors (48%) had a median survival of 4 ± 3 months. Upon these bases, it is possible to select the best candidates for curative resection, those for whom an aggressive treatment should be mandatory, from those who will not benefit from hepatectomy. All together, they represent 40–55% of cases. In the middle one finds the huge group of cases presenting one risk factor. They do not display an astonishing survival performance (median survival is around 8–9 months). Yet among these it is possible to find long-term survivors. We think that in these cases the therapeutic decision should be discussed on a case by case basis, considering that a major prognostic factor emerging from the literature is represented by the possibility to achieve a curative resection.

The second point we want to discuss concerns the

different prognostic factors in the subgroup of patients submitted to hepatectomy. Two of them have special importance. Gastric cancer progression through the serosa (T4) is a negative prognostic determinant that must always be considered, as it opens the door of the peritoneal cavity (5,12-14). Beside this, we would like to insist here that the completeness of tumor bulk removal is the key-point of the therapeutic strategy. The expansion of the experience and the most recent series focusing on surgical subgroups, indicate this point precisely. In a recent review of our cases (5), we were surprised by the absence, once excluded the factor T of the gastric primary, of other gastric cancer or metastasis-related prognostic variables emerging from our data. Indeed, this enhances the surgeon's role in the management of these cases.

In the synchronous setting R0 resection must be achieved both on the hepatic metastases and on the gastric primary, thus gastrectomy must be routinely associated to $D \geq 2$ lymphectomy.

In our experience, once R0 resection can be achieved, the extent of hepatic involvement no longer influences the prognosis. This finding is in contrast with data from some of the most numerous cohorts published (6,8,10,15,16) but merits full attention. From a speculative point of view, this enforces the idea that hepatic metastases may still be included in the concept of regional disease, which may benefit from regional surgery. This concept is well validated for metastases from colorectal cancer, but it is absolutely new for metastases from gastric cancer.

The third point concerns the prognostic role displayed by the timing of metastatic disease.

Clinicians consider the metachronous presentation as more favorable. The conclusion of the commented meta-analysis seems to contradict this certitude. It must be noted, however, that they only considered the 5-year survival and not the entire survival curve. Patients submitted to hepatectomy for metachronous metastases benefit of a better selection and display better survival performance in the short and medium term; at 5 years, however, survival curves tend to approximate each-other (5).

Concluding this editorial we'd like to comment the observation by Markar and co-authors concerning the limits of literature as far as the performance status and co-morbidity of studied patients are considered. We are confident that in this phase the majority of surgeons reserved their attention to the best patients, those fit for surgery and with the more favourable hepatic involvement. We fully appreciate the scientific biases linked to these limits

but also the results emerging from the simple, common-sense oriented clinical practice. These results encourage the surgical treatment of these cases, at least in the best conditions. The biologic impact of this kind surgery is also unknown, but we noted in our outpatient activity that the postoperative period is easy, that patients perform well and are generally satisfied of the treatment they received. These are all the reasons that encourage our activity in promoting this relatively neglected topic.

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Footnote

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