To resect or not resect in metastatic gastric cancer: that is the question!

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Last week we discussed 5 patients with gastric cancer at a meeting of our interdisciplinary tumor board. With the evidence we have and the recent publication of multidisciplinary treatment guidelines [1, 2] most decisions were easy to take and we achieved a great consensus with our colleagues from surgery and radiation oncology about our treatment standards. But one case concerned us a lot and we do not know yet if we took the right decision.

A 46-year old man, born in Russia who had emigrated to Germany as a child—a freelance carpenter and father of 2 children—presented 5 months ago with a swollen painless lymph node at the right side of the neck. Histopathologic assessment revealed an adenocarcinoma of the intestinal type. Further examination showed a distal stomach cancer infiltrating the duodenum, two borderline enlarged lymph nodes in the mediastinum, and several enlarged lymph nodes along the aorta from the diaphragm down to the iliac bifurcation. These nodes were all positive on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). We treated this patient with docetaxel, 5-fluorouracil, and cisplatin [3]. He tolerated the treatment well but then he developed sensory neuropathy in the fingers and toes during the last cycle and complained about increasing taste disorder and about fatigue. The last computed tomography (CT) scan showed a good response in the lymph nodes. The mediastinum was normal and some enlarged lymph nodes in the retroperitoneum were no longer avid for FDG on the

PET-CT. On endoscopy we still found a vital non-obstructing tumor in the distal stomach infiltrating the descending part of the duodenum. The patient had no difficulties in feeding himself and did not complain about vomiting or a sensation of fullness.

Should we recommend secondary surgery for this patient? And if we do, exactly what kind of operation should the surgeon do? Our surgeon explained to us that due to infiltration of the duodenum the minimal requested procedure would be gastrectomy plus duodenectomy and partial pancreatectomy. He asked us if this far-reaching procedure was really justified in the light of the initial spread reaching from the neck down to the iliac bifurcation? At the end of a long discussion we decided to go back to the patient, and explain to him the technical and biological difficulties associated with his particular situation and not recommend a secondary gastrectomy for him.

Did we take the right decision? The article written by Kanda and colleagues in this issue of the journal [4] reports on a cohort of 28 patients with advanced gastric cancer who were not eligible for a primary surgical treatment and who were treated with secondary surgery. The patients had T4 tumors or distant metastases of the para-aortic lymph nodes, the peritoneum, or the liver. All the patients had received primary chemotherapy based on S-1, which is an oral fluoropyrimidine currently not available outside East Asia, where this compound has shown high efficacy [5]. The cohort investigated in Kanda's study were able to safely undergo secondary resection, with the resection often being "complete" in terms of having formally achieved an R0 status, and the overall survival was reasonable and better than would have been expected with chemotherapy alone. Initial tumor size and depth of infiltration, lymph node involvement, and response to systemic treatment were the factors that were associated with a

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better prognosis. These findings are provocative and may guide us in the direction of thinking more often about secondary surgical approaches in advanced gastric cancer, as we already do in other tumors such as colorectal cancer. But who exactly was chosen for this approach in Kanda's study?

Japan is one of the countries with the highest incidence rates of stomach cancer worldwide. Twelve hospitals, mostly large academic institutions, were involved in the study carried out by Kanda et al. These authors observed their procedures over a time period of 8 years and have now reported on 28 individuals. Arithmetically, they recommended secondary gastrectomy for one patient every 3.4 years per institution. This is reflective of an extreme patient selection and does not really help us in finding the right patients in our populations who may benefit from secondary gastrectomy or metastectomy. We are faced with an individual decision that we have to take together with our colleagues working together in a multidisciplinary team and—of note!—working with the patient in due consideration of all possible risks and the unknown benefit.

In Kanda's study it was shown that secondary surgery can be offered with reasonable morbidity. But this surgery is never without risks and these may even be lethal. The experienced Japanese surgeons also encountered some severe complications, including pancreatic fistula, intra-abdominal abscess, and anastomotic fistula. The maximal hospital stay was 86 days, this not being an inviting perspective for someone who faces death and who is likely to have no more than some months to live.

Nevertheless, surgery may have a complementary role in the management of advanced stomach cancer in selected groups of patients. We should not be completely discouraged by the generally dismal prognosis of this disease. The situation is certainly different compared with that for colorectal cancer, where we routinely do hepatectomies and other surgical procedures when managing patients with metastatic disease [6]. With the advent of more active chemotherapy in colon cancer it is now under discussion when to go for primary chemotherapy, when to go for primary surgery, and when or in which sequence to combine both approaches. Conversion chemotherapy has become a new goal in "colorectology", meaning the conversion from a poorly resectable metastatic status to a completely resectable status by using maximally active chemotherapy-antibody combinations [7]. But there is no reason to exclude subgroups of patients with advanced gastric cancer that may benefit from surgical treatment in the light of the advent of more active chemotherapy regimens and the implementation of targeted drugs that may be active in specific gastric cancer subtypes [3, 8, 9]. The current understanding is that metastatic gastric cancer

should be treated with chemotherapy and never with surgery alone. Maybe the term "conversion chemotherapy" is inappropriate for the situation of advanced gastric cancer. But surgical treatment in addition to medical treatment might be of benefit under certain circumstances.

What circumstances are these? In order to have a clear answer, a better understanding of the natural course of the disease will be necessary. Some prognostic clinical factors have been established and may lead us to find the right patients for more invasive forms of treatment [10]. But more and better outcome research in metastatic gastric cancer is necessary. Prognostic factors going beyond what we currently know could be established, including molecular signatures [11–13], and also molecular imaging of the tumor and the patient's immune status may play a role.

What kind of studies do we need? Kanda and co-authors propose performing a prospective randomized study on the topic of secondary surgery in metastatic gastric cancer. It seems unlikely to us that such a study will ever come about, because the heterogeneity of the disease extension and, therefore, the potential selection criteria for such a study seem just too wide. But an international register of "extended surgical procedures" in gastric cancer could be a good start. If this was accompanied by sampling of tumor tissue and blood probes we could establish a robust database to build on. We have discussed this idea within the European Organization of Research and Treatment of Cancer Gastrointestinal Tract Cancer Working Group, but action still has to be taken.

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