Oligometastases of Gastrointestinal Cancer Origin

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Question 1: What is the rationale for a liver-first approach in synchronous colorectal liver metastases and in which treatment algorithm should it be integrated?

Büchler/Ulrich: There is no evidence that either liver-first or primary-first concepts have any advantage. We currently prefer to resect the primary first and perform the liver resection 8–10 days later during the same hospital stay if the liver metastases are resectable. In case of metastases in all segments, we investigate the liver during the resection of the primary and evaluate if one side of the liver – most times the left side – could be freed from metastases by atypical resections. The ligation of the contralateral portal vein is also evaluated. A couple of weeks later, the resection of the liver metastases could be completed. In case of non-resectable liver metastases, a conversion chemotherapy should be tested first. When there is resectability after 4–5 cycles of chemotherapy, the liver resection should be performed first, followed by the resection of the primary later.

Lang/Mittler: The rationale for the liver-first approach is a liver resection of limited hepatic metastases before a systemic, potentially hepatotoxic chemotherapy is implemented in a multimodal treatment setting. Decision making depends on the extent and distribution of the disease. Algorithms should separately consider colonic and rectal carcinoma due to different multimodal strategies for each disease.

Lordick: We are using a liver-first approach in Leipzig, and most often the reason for going for ‘liver-first’ is that the curative ap-

proach could be limited by the resectability of hepatic disease rather than by the primary tumor. This is synchronous metastatic colorectal cancer, a condition with a critical prognosis, even if complete resection of all lesions is possible. For this reason, the majority of patients also receive systemic chemotherapy which we often start upfront, i.e. 3–4 months before the planned liver surgery. Chemotherapy induces a good response in >50% of the patients. If we use highly active regimens like FOLFIRINOX, response rates may even rise to 80%. This treatment sequence gives us the opportunity to avoid futile liver resection if the disease is highly aggressive, which means that it is rapidly progressive during induction chemotherapy and that extrahepatic metastases occur.

But to be honest: The scientific evidence for this sequence is scarce. Results from prospective randomized controlled trials are lacking, and other sequences may also be well justified and as effective as our approach. We are on the level of expert knowledge and publications of relatively small series of patients, most often done as retrospective studies in high-volume centers. The majority of patients with stage IV colorectal cancer in Europe, however, is not treated by experienced teams but in small-volume settings. This is a problem. Experienced teams take better decisions. We see many unusual treatment approaches when patients present for second opinion at our center. They often come when some part of treatment has already been done at small centers, like resection of the primary tumor or several months of any chemotherapy. The point is that deciding the best treatment strategy for synchronous metastatic colorectal cancer requires expertise and knowledge. These patients are best referred to experienced academic centers upfront where an experienced multidisciplinary tumor board can discuss their situation based on optimal imaging assessment.

Torzilli: Managing primary and metastatic hepatic tumor simultaneously is generally considered more risky [1]. Then, except for conditions featuring a symptomatic colorectal disease, which demands treatment, or conditions of easily resectable oligometastatic disease, the priority regarding a prognostic standpoint is determined by the liver involvement [2]. In the event that the liver is involved even with a few metastases but featured by complex intrahepatic location, a liver-first enhanced one-stage hepatectomy (e-OSH) should be preferable [3], since the association of a complex hepatectomy with colorectal surgery could be too risky. Therefore, e-OSH assimilates a staged surgery in a liver-first attitude when synchronous disease exists [4]. Inversely, in a staged hepatic clearance, the first stage to the future remnant liver could be associated with the removal of the primary tumor [5], limiting in fact the need of a liver-first approach. The difference between a 'staged' e-OSH and two-stage hepatectomy with associated primary tumor removal at the first stage is possibly the fact that, with the liver being the organ which determines the surgical feasibility in most cases, dropout would be less frequent from a single-stage liver clearance perspective compared to those with the liver cleared in two steps [6]. Therefore, whenever a liver-first approach would be preferable, an e-OSH followed by colorectal surgery at the second stage seems the most reasonable approach.

Vauthey/Mizuno: The liver-first approach is preferred as long as the patients have no obstructing primary tumor because i) liver resection carries a lower incidence of wound infection and no risk of anastomotic leakage compared to resection of colorectal primary, and ii) progression of liver metastasis drives the prognosis of patients with stage IV colorectal cancer.

Question 2: Regarding synchronous liver metastases from pancreatic ductal adenocarcinoma: Which patients benefit most? What are the predictors for improved outcomes? Are they validated?

Büchler/Ulrich: There are two scenarios:

- (1) The synchronous liver metastases are detected first during the surgical exploration. In young patients and in those with few comorbidities, we might continue with the resection (including the liver metastases) if no other unfavorable aspects are apparent (e.g. arterial involvement...) and a maximum of three easily resectable metastases is detectable by intraoperative ultrasound. This procedure has been recently evaluated in two retrospective studies – one multi- and one single-center experience – and shown to improve survival in selected patients [7, 8].
- (2) The liver metastases are known prior to surgery. In these cases we would transfer the patients to chemotherapy with FOLFIRINOX and would mandatorily re-evaluate the patients after 4–6 cycles. In case of stable disease or regression, the patients should be surgically explored despite the presence of metastases [9]. Currently there are no validated predictors of improved outcome for patient selection. A recent Italian study, however, suggests that a decrease in CA 19-9 of more than 50%

and a maximum number of five metastases after completion of an induction multi-agent chemotherapy could be two parameters that should be considered [9]. These patients seem to have a more favorable outcome. As this study only included a very small number of patients, further validation is certainly warranted to define patients who benefit from this procedure.

Lang/Mittler: Hackert et al. recently demonstrated that combined resection of the pancreatic primary and synchronous liver metastases was associated with a median survival of 11 months as compared to 14 months in patients with metachronous metastases. In highly selected patients who responded to prior chemotherapy, Crippa was able to demonstrate a 3-year overall survival of >50% as compared to 10% in patients who were chemoresponders but did not have surgery. Apart from that, to our knowledge, there are no well-established or even validated outcome predictors.

Lordick: All knowledge about these procedures is based on nothing more than case series. From a scientific viewpoint, they confer the risk of selection bias, underreporting of unfavorable outcomes, and overestimation of the benefits of surgical treatment. A prospective comparison with alternative forms of treatment like systemic chemotherapy alone or ablative techniques other than surgery is lacking. No validation studies have been done. In one of the biggest series published by colleagues from Paul-Brousse hospital in Paris [10], patients with pancreatic cancer who underwent liver resections were in prognostic group 2 (together with gastric cancer) and achieved a 5-year overall survival rate of 15–30%, which does not sound too bad for this disease. However, synchronous disease was a poor prognostic factor, as was extrahepatic disease, resection of more than two segments of the liver, incomplete resection, and patient age older than 60 years. I believe that patients who are willing to undergo liver resection for pancreatic cancer must be made aware of the limited evidence. They must know that this is not a standard treatment and that the risk-benefit ratio is unknown. In our center, we select patients very carefully for liver resections and we do not aim for a 'surgery-first' approach in synchronous disease. We consider it, though, on an individual basis, in patients who have resectable disease after 3–4 months of induction chemotherapy. We do not promise cure because this treatment goal is unrealistic in metastatic pancreatic cancer.

Torzilli: Retrospective multi-institutional [7] or prospective monocentric [8] studies have shown some potential benefit in terms of long-term prognosis of simultaneous resective surgery with respect to shifting the patient to palliation. These initial reports convey important insights to be validated: i) the long-term survivors exist; ii) morbidity and mortality do not seem to outrange those of simple pancreatectomies. Room for prospective trials run by tertiary referral centers and for patients with synchronous, oligometastatic, and easily resectable liver disease could be seen.

Vauthey/Mizuno: There is no benefit of resection in such patients.

Question 3: Is it justified to extend the indication for resection of metachronous metastases of pancreatic ductal adenocarcinoma on the basis of a better prognosis than the resection of synchronous metastases?

Büchler/Ulrich: To date, there is no evidence that the survival time after resection of metastases differs between synchronous and metachronous resection from the time of the metastatic resection itself. However, in the metachronous setting, the time between primary tumor resection and metastatic resection has to be added, resulting in a longer overall survival. Consequently, if metachronous metastases develop later than 12 months after primary resection, this underlines a favorable tumor biology, and resectability should be evaluated and probably pursued in a larger number of patients than in the synchronous situation, if possible. Mainly, as a 5-year survival of 10% can be achieved, an extension of indication seems reasonable, while the proper patient selection remains the challenge.

Lang/Mittler: In our own experience, the time intervals between resection of the primary and detection of the metachronous liver metastases was rather short. Half of our patients had liver metastases after 1 year and no patient after 2 years. This early occurrence of metachronous metastases challenges this concept for this cancer entity and would go along with the rather similar resection outcome in patients with either metachronous or synchronous metastases recently demonstrated by Hackert.

At this point, the decision to resect is made on a highly individual basis.

Lordick: Synchronicity of metastatic disease is a poor prognostic factor. This needs to be taken into account when weighing the potential benefits and risks of surgical treatment in patients with stage IV pancreatic cancer. The longer the time interval between the primary diagnosis and the occurrence of metastases is, the more we would tend to recommend ablation or resection of a liver metastasis.

Torzilli: Considering the fact that, as a general understanding, metachronous metastases have a better prognosis than synchronous ones, recalling what asserted my answers to question number 2 in relation to some encouraging reports about synchronous metastases from pancreatic cancer [7, 8], and having gathered sporadic but encouraging data for metachronous presentations from the few literature reports [11, 12], the answer should be 'yes'. Again, as for the synchronous presentations, limiting such activity to tertiary referral centers with well-established selection criteria should be the way of facing this issue.

Vauthey/Mizuno: Resection may be beneficial in exceptional patients with solitary metastasis in the context of response to systemic therapy.

Question 4: What is the goal of surgical resection of non-colorectal hepatic oligometastases?

Büchler/Ulrich: The main goal should be to remove all visible metastases by surgery. A combination of surgery and interventional approaches has been described in small series as well [13]. As the benefit of these combined liver-directed therapies is still unclear, the main goal should be a complete surgical removal to increase the survival time of the patients with also improved quality of life. However, cure can only be achieved for a small subgroup of patients.

Lang/Mittler: Analogy from colorectal liver metastases to non-colorectal disease can be drawn by taking into account the tumor entity and individual risk factors according to the prognostic model by Adam et al. [10]. In patients with resectable oligometastases limited to the liver, the primary goal of resection is curation. A secondary goal is the achievement of chemotherapy-free intervals.

Lordick: Accepted treatment objectives in oncology are: i) to achieve cure, ii) to achieve prolongation of survival, and iii) to achieve a better symptom control and quality of life. There is probability that surgical treatment can achieve cure in patients with non-colorectal and non-endocrine gastrointestinal cancers. However, 5-year survival rates of around 30–35% have been reported in very selected patients, with 5-year relapse-free survival rates around 15%. This does suggest that some (few) patients have a survival benefit from treatment. However, we do not know the survival outcomes if this group of patients with favorable prognostic characteristics has been treated non-surgically. Symptom control and quality of life, the third goal, has not been systematically reported. Therefore, we simply do not know if the potential benefits of surgery outweigh the potential risks and side-effects.

Torzilli: As usual, it should prolong the patients' survival although for some of them (i.e. NET) debulking could be an endpoint, too; indeed, reducing the tumor burden seems to enable an improvement of symptoms and to control disease progression [14–16]. Until now, there is no definite answer to this as such, and probably it will not be available in the near future. What is more, the rarity of the disease and the patient's low likelihood to take part in such studies limit their feasibility. Personally, I believe that, whenever feasible, surgery should lead to complete liver clearance, particularly when an attitude to parenchyma-sparing approach is already part of the team's practice.

Vauthey/Mizuno: It depends on types of primary tumor. For example, in patients with neuroendocrine liver metastases, liver resection reduces symptoms associated with functional tumors and provides meaningful therapy- and disease-free survival and may prolong overall survival.

Question 5: How realistic is the achievement or extension of chemotherapy-free intervals by liver resection of oligometastases?

Büchler/Ulrich: Even though liver metastases recur in almost 80% of the patients, the chemotherapy-free intervals can be increased, especially for colorectal cancer patients.

Stage IV pancreatic cancer would usually require lifelong chemotherapy in most patients. However, chemotherapy-free intervals might be debatable once a metastatic resection was performed and the adjuvant treatment protocol completed. Until a progression locally or with new metastases, patients would not necessarily require chemotherapy.

Lang/Mittler: As demonstrated by Adam et al., 36 and 23% of patients after resection of non-colorectal liver metastases survived 5 and 10 years, respectively. About half of these (16 and 10%) did so without recurrence. In these patients, resection provided long-term freedom from chemotherapy, and there are more patients who realistically benefit in this regard at least on a short-term or midterm basis. In our experience, this is especially true for mono- or oligometastases limited to one organ.

Lordick: The achievement of chemotherapy-free intervals is not an accepted treatment goal per se. I see the point, though, that some patients may wish to have a break from chronic chemotherapy. The question is: Do we need surgery to give patients a break from chemotherapy? Sometimes, breaks from chemotherapy under close observation can also be achieved without going for invasive treatment first.

Torzilli: It is more than a hope. Rather, it is a real achievement, as confirmed by the study by Nordlinger et al. [17] in which perioperative chemotherapy did not prove to be superior in terms of long-term survival than surgery alone for patients with oligometastatic liver disease from colorectal cancer.

Vauthey/Mizuno: It may be influenced by several factors: types of primary cancer, tumor biology, and response or adverse effects of systemic therapy or alternative local therapy other than resection.

Question 6: What is the intraoperative decision making after incidental discovery of hepatic oligometastases at laparotomy for resectable pancreatic cancer or gastric cancer?

Büchler/Ulrich: In young patients and in those patients with few comorbidities, we might continue with the resection (including the liver metastases) if no other unfavorable aspects are apparent (e.g. arterial involvement ...) and a maximum of three easily resectable metastases is detectable by intraoperative ultrasound. A combination of either gastrectomy or pancreatoduodenectomy with a synchronous major hepatectomy does not seem to be recommendable due to a considerable risk of morbidity and even postoperative mortality.

Lang/Mittler: In our experience, incidental discovery of hepatic oligometastases upon primary laparotomy (i.e. synchronous metastases) is a rather rare event. For pancreatic cancer, we would abort the procedure after confirmation by frozen section histology.

In gastric cancer, and in the setting of incidental resectable hepatic oligometastases, we would go for a combined simultaneous or staged resection, in an either stomach- or liver-first approach. Resection should be embedded into a multimodal strategy. In gastric (and esophageal) cancer with preoperatively detected limited hepatic metastases, inclusion into the 'Renaissance Flot 5' trial can be considered.

Lordick: I am not a surgeon, but actually we try to avoid this situation as much as we can because decisions at this point seem to be difficult to take. In our center, we do meticulous staging, following the guidelines, before we go for cancer surgery. Most patients with gastric cancer undergo diagnostic laparoscopy to exclude peritoneal and liver involvement, and if we find it we are going for specific approaches in the framework of clinical trials, if available (like the current GastriPec trial for gastric cancer with peritoneal involvement). In case of pancreatic cancer, if a single incidental resectable liver lesion occurs, our surgeons tend to resect it together with the primary tumor and we would offer the patient adjuvant chemotherapy for 6 months, knowing that relapse risks are statistically higher than with stage I–III disease.

Torzilli: In a tertiary referral center, refraining from surgery would not be the obvious reply, upon recalling the data related with surgical resection for pancreatic cancer [7, 8]. Similarly, challenging gastric cancer metastases seems to be an option after preoperative chemotherapy, while excluding non-responders or unresectable patients [18]. The complexity of liver involvement in terms of number, location, and relation of the metastases and also the local advancement of the primary cancer should be factors regarding decision making. In this sense, the effort of defining selection criteria in order to enable surgery for those patients who may benefit more from an aggressive surgical approach in spite of the synchronous involvement of the liver should be a priority. In this regard, the lack of a commonly shared definition of resectability drastically limits any attempt of standardization [19].

Vauthey/Mizuno: There is no indication for resection.

Question 7: More data are needed on surgery for oligometastases, but for well-known reasons patients remain scarce. Would you rather support an international registry instead of controlled studies to generate more evidence?

Büchler/Ulrich: We would support controlled studies.

Lang/Mittler: For controlled trials needed for each tumor entity, it will be difficult to find a sufficient number of patients in order to

obtain a significant statistical power. We therefore support the idea of an international registry although the evidence arising from even large registries is limited.

Lordick: Randomized controlled trials are the gold standard for increasing the scientific evidence. However, phase III trials are expensive, and funding for academic research is difficult to achieve. Often, these questions cannot be answered on a national basis, but funds from national resources (like Deutsche Forschungsgemeinschaft (DFG)) often do not allow for inclusion of patients from abroad. This is a dilemma, while it is true that these patients are difficult to find. To give an example: Yonsei University from Seoul, South Korea, a leading center for treatment of gastric cancer in Asia, published about a subgroup of 22 patients who underwent 'curative gastric resection and liver resection' and achieved long-term survival in every fifth patient [20]. These 22 patients were selected from 10,259 patients who presented with gastric cancer at this center in the respective time period and from 1,013 patients

who presented with liver metastases for gastric cancer. These numbers illustrate the magnitude of the problem to get more insights. And do we believe that all these 22 patients would have consented to undergo random allocation to surgical versus non-surgical treatment? And that all of them would have met the strict selection criteria for being enrolled into a prospective randomized controlled trial? For this reason, within the European Organisation for Research and Treatment of Cancer (EORTC), we are currently creating a joint international prospective registry trial in cooperation with the Japan Clinical Oncology Group (JCOG) to join forces with two of the most powerful clinical research groups worldwide.

Torzilli: That sounds more than reasonable.

Vauthey/Mizuno: A multicenter molecular biology-based registry may contribute to define the subsets of patients who are the best candidates for liver resection.

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