Visceral Medicine

Interdisciplinary Discussion

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Precision Medicine

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Lordick: Surgery, Local Ablation, Interventional Techniques, and Systemic Chemotherapy in Oligometastases of the Liver – When to Use Which Technique and How Would a Multimodal Concept Look Like?

Ghadimi:

This depends on the tumor type, patient characteristics, dynamics of tumor disease, time span from primary diagnosis to metastases, metastasis location, and number of metastases. It also depends on the type of metastatic disease, i.e., synchronous or metachronous.

Gockel:

As the biology of oligometastases is decisive for the treatment algorithm, prognostic information (e.g., the holistic context of the disease stage) and predictive parameters (e.g., selection of a primary systemic vs. ablative therapy) are essential to the clinician. According to the ESMO Consensus Guidelines, oligometastatic disease (OMD) is characterized by the presence of metastases at up to 2 or occasionally 3 sites and no more than 5 (or sometimes more) lesions, predominantly visceral [1]. Irrespective of the primary tumor entity, systemic therapy is generally the standard of care, and it should be considered as the initial strategy. Exceptions are patients with single (few) resectable liver (or lung) metastases. The specific type of treatment depends on (i) exact OMD localization, (ii) the treatment goal (e.g., the more curative intent, the more application of surgical resection; importance of local vs. systemic control), (iii) local expertise and availability, (iv) treatment-related morbidity, as well as (v) patient comorbidities and biological age, and (vi) recurrence of OMD in the same organ.

The multimodal concept in our own clinical practice is as follows: (1) induction (chemo)therapy with response evaluation (e.g., 6–8 weeks after treatment start), (2a) surgical resection first in patients with manageable surgical risks and comorbidities or, alternatively, (2b) a "toolbox" of local ablative methods: RFA (radiofrequency ablation) > MWA (microwave ablation) > IRE (irreversible electroporation). Cryoablation is not performed in our center. High-precision radiotherapy, such as SBRT (stereotactic body radiotherapy), is noninvasive and has no "heating effect" – with respective advantages. In case of palliative intent, locoregional treatments with embolic techniques, such as radiotherapy (SIRT [selective internal radiotherapy) or chemoembolization (TACE [transarterial chemoembolization)/beads) are applied.

Graeven:

I think the concept of multimodal therapy in OMD is best established in colorectal cancer and should be considered standard of care for those patients. In esophageal/gastric cancer, this concept has gained more and more acceptance. In pancreatic cancer, the concept of a multimodal approach in OMD is in my opinion limited to very rare and selected cases.

In addition to the localization of the primary cancer, it is also important to differentiate between synchronous or

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metachronous metastases. A colorectal cancer patient who presents with metachronous liver metastasis would be reviewed by an interdisciplinary tumor board. Our first option would be surgical resection. The second option would be whatever technique seems suitable to destroy the metastasis or for which the best local expertise exists. If no local approach is promising, we would opt for a systemic therapy, i.e., complete resection or destruction of the metastasis, according to the pathological characteristics of the tumor. These patients would be re-evaluated routinely for secondary resection within the interdisciplinary tumor board. In synchronous metastases, an option could be to start with systemic therapy to test the biology of the disease; patients that progress under a presumed active systemic therapy would have rarely benefited from surgery of liver metastasis, for example, whereas patients that do not progress during this "induction" therapy may well be candidates for local measures.

Westphalen:

This is a very broad question and nearly impossible to answer on a general level. In the end, the ultimate goal is to achieve liver clearance to improve individual patient outcomes. To reach this goal, it is imperative to work in a multidisciplinary team to implement all tools available in the patient's best interest.

Lordick: Molecular Tumor Board: Still Research or Already Clinical Routine?

Ghadimi:

It depends on the tumor type. In lung cancer, it is routine for certain subtypes. In pancreatic cancer, I rather think that is still research.

Gockel:

A molecular tumor board is already clinical routine, with weekly meetings.

Graeven:

I think that for gastrointestinal tumors, the information for those few molecular markers that for the moment impact the decision for systemic therapy can easily be integrated in a regular interdisciplinary tumor board. This might change in the future when we identify more specific mutations or patterns of resistance to molecular therapeutics like, for example, in lung cancer. For the moment, I believe we do not need a separate molecular tumor board for gastrointestinal cancer.

Westphalen:

With the rapidly increasing use of comprehensive genomic profiling in oncology, novel ways to integrate testing results into clinical care are needed. In my opinion, molecular tumor boards close this gap in our health care system as they incorporate therapeutically relevant testing results into a multidisciplinary care plan. Furthermore, they serve as an important "knowledge hub" to distribute information on the chances and challenges in precision oncology. Furthermore, as more and more molecularly guided therapy options become available, precision oncology programs and molecular tumor boards can serve as important screening platforms for innovative clinical trials. All of these activities are labor and time intensive; accordingly, molecular tumor boards have not been established uniformly. However, this does not mean that these clinical structures can be considered research activities.

Lordick: Which Biomarker Do You Use Routinely for Precise Stratification of Treatment in Patients with Gastric, Pancreatic, and Colorectal Cancer?

Ghadimi:

- *Gastric Cancer.* MSI, PDL-1, HER2-Neu, and EBV.
- *Pancreatic Cancer.* We routinely analyze a multigene panel of >80 genes for research purposes. In single patients, this has a therapeutic effect.
- *Colorectal Cancer.* MSI, BRAF, RAS

Gockel:

- *Gastric Cancer.* (1) HER2-Neu amplification: stratification according to the HER2-Neu status. The EORTC 1203 INNOVATION study evaluates if the HER2 antibodies trastuzumab or trastuzumab/pertuzumab in combination with perioperative chemotherapy improve disease-free survival (NCT02205047) [2]. (2) MSI-H (microsatellite instability-high): first analyses question the efficacy of perioperative chemotherapy in patients with MSI-H status [3]. MSI is assessed in routine practice. However, it is still discussed with controversy if patients with resectable MSI-H gastric cancer should undergo perioperative chemotherapy [4]. Studies designed specifically for MSI-H localized gastric cancers are warranted. (3) Claudin 18.2: claudin is determined in primary metastatic or recurrent gastric cancer/adenocarcinoma of the distal esophagus, and patients are evaluated for the SPOTLIGHT study (phase III efficacy, safety, and tolerability study of zolbetuximab plus mFOLFOX6 chemotherapy compared to placebo plus mFOLFOX6 as treatment for gastric and gastroesophageal junction cancer) (NCT03504397).
- *Pancreatic Cancer.* (1) *KRAS:* the most common mutation in ductal adenocarcinoma (>90%) is KRAS oncogene. In patients with KRAS wild type (WT), panel sequencing is performed, and they are included, if eligible in the NCT (National Center for Tumor Diseases) master program. Routinely, we screen patients with advanced disease for the presence of NTRK fusions

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and MSI. *(2) BRCA1/2:* BRCA is the most frequent mutation in familiar pancreatic cancer and detected in about 5%. In these patients and in a subgroup of sporadic cancers, targeted therapies with PARP (poly[adenosine diphosphate-ribose]polymerase) inhibitors are now approved. BRCA1/2 alterations are analyzed routinely in our center. Olaparib is offered to patients with metastatic pancreatic cancer who are clinically stable for a minimum of 4 months during platinum-based first-line chemotherapy, although published data have not yet been able to demonstrate a benefit in overall survival [5]. With longer follow-up, hopefully, a more consistent benefit will also become visible. Another intent of BRCA analysis is response prediction to conventional chemotherapy (especially to FOLFIRINOX) and to targeted therapies.

– *Colorectal Cancer.* (1) *KRAS mutation (MT):* MT of exons 2, 3, and 4 → negatively predictive; no proven efficacy of anti-EGFR therapy. (2) *NRAS MT:* MT of exons 2, 3, and 4 → negatively predictive; no proven efficacy of anti-EGFR therapy. (3) *RAS WT:* positively predictive; anti-EGFR antibodies → in left-sided RAS WT tumors. (4) *BRAF V600E:* negatively predictive; BRAF and MEK inhibitor + combination with anti-EGFR therapy: BEACON study. (5) *MSI-H:* positively predictive; immune checkpoint inhibitors (PD-1, PDL-1, and CTLA4 inhibitors), particularly in familiar colorectal cancer testing of hereditary cancer and Bethesda criteria; stage III: adjuvant immune therapy (ATOMIC study). (a) Monotherapy: pembrolizumab and nivolumab (metastatic colorectal cancer) and (b) combination therapy: nivolumab and ipilimumab (after oxaliplatin and irinotecan). (6) *NTRK1–3 fusions:* larotrectinib or entrectinib in second-line therapy. (7) *HER2 amplification:* negatively predictive for anti-EGFR response (resistance mechanisms) and potential efficacy for trastuzumab and pertuzumab. (8) *cfDNA/ctDNA:* in liquid biopsies; colorectal cancer stage II: CIRCULATE study. Third line metastatic colorectal cancer: FIRE4 study. RAS-MT analysis in liquid biopsies predictive for re-induction of anti-EGFR therapy.

Graeven:

Gastric Cancer. We routinely ask for the HER-2 and MSI status. For pancreatic cancer, we integrate the BRAC-1 status and MSI in our decision in the metastatic setting. For patients with colorectal cancer, we ask for the all-RAS, BRAF mutation status, MSI, and HER-2.

Westphalen:

Generally, we run comprehensive molecular profiling with next-generation sequencing panels for a significant proportion of patients in the beyond-first-line setting. Accordingly, we cover most standard and experimental biomarkers at some point for all our patients.

Standard of care is HER2, EBV, MSI, and PDL-1/CPS score for gastric cancer and all-Ras, BRAF, and MSI for colorectal cancer. For pancreatic cancer, all patients undergo next-generation sequencing at initial diagnosis of metastatic disease. We aim to identify BRCA1/2 alterations and Kras WT patients and other rare therapeutic targets. Furthermore, all patients are tested for MSI.

Lordick: What Is the Biggest Challenge in Establishing Precision Medicine in Visceral Oncology?

Ghadimi:

(1) Randomized clinical trials (basket trials) and (2) relevant biomarkers with reliable targets and effective drugs.

Gockel:

The biggest challenges of precision medicine in visceral oncology are: molecular heterogeneity of tumors, including intratumoral heterogeneity, and low frequency of some targetable molecular alterations in general (e.g., NTRK fusions in many common cancers). Consequently, the "real" prognostic benefit for single patients has to be evaluated with continuous caution, while establishing precision medicine. More basket trials on molecular-targeted agents are needed, as single studies are not able to recruit adequate numbers of patients timely. With respect to precision surgery, the challenge remains to identify patients who become resectable following induction/conversion chemotherapy and to define more radical surgical indications for patients with metastatic disease.

Graeven:

I believe that the concept of targeted medicine is fully accepted in visceral oncology. The main problem, however, is the limited number of druggable targets. Therefore, we have continuously to strive for a better understanding of the underlying tumor biology. The same holds true for immune oncology in visceral oncology where we need to understand how we can make microsatellite-stable tumors suitable for immune oncology treatments.

Westphalen:

There are multiple challenges in the implementation of precision oncology (in visceral medicine) [6]. Personally, especially in the setting of multiple novel therapeutic modalities being approved or being in late-stage clinical development across most entities of gastrointestinal cancers, I believe that we now have to find ways to pave the way for structured access to quality-assured comprehensive genomic profiling in the setting of dedicated structures. This will allow for optimal integration of testing

results into the clinical management of the individual patient. Establishing such structures will require transsectoral work including – but not limited to – health care professionals, health technology assessment/regulatory agencies, and payers.

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