The Role of Image-Guided Oncology and Local Tumor Treatments

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Question 1: Professor Pech, what does the future of local tumor ablation look like? What is the rationale behind it?

Pech: There are indeed distinct limitations of thermal ablation such as radiofrequency ablation (RFA), despite RFA being the most frequently used local ablation tool available. However, in many cases anatomical locations with adjacent thermosensitive structures or the size of a specific lesion represent strong limitations in daily routine, requiring more efforts in the development of non-thermal ablation techniques. Ultimately, the toolbox enabling minimally traumatic local treatments will be decisive for patient outcome – in a patient selection beyond what is considered suitable for local approaches today. However, even today the combination of thermal ablation, resection, and radiation allows extensive macroscopic tumor cell count reduction in almost all patients considered 'oligometastatic'.

Local tumor ablation may strongly improve the outcome of systemic chemotherapies or targeted treatments. According to the Goldie-Coldman hypothesis from the 1970s (!), extensive local treatment (with reasonable interventional risk) reduces the mathematical probability of a chemotherapy-resistant clonal selection. Hence, local tumor ablation or local treatment in general promotes an optimal environment for simultaneous chemotherapy – it may even help to suppress resistant clones if used in between chemotherapy cycles (in biologically suitable candidates!). In the CELIM study [1], patients resected R0 or ablated completely after downstaging had almost twofold survival rates as compared to R1-resected patients. Maybe there is a selection bias in that study; however, would this result not best be explained by clonal selection pressure through complete resection?

**Question 2: Local tumor ablation in combination with chemotherapy would undoubtedly result in the best imaginable 'deepness of response'.
If deepness of response truly works, such as proven for colorectal metastases [2], what would you recommend to your patients if the procedural risk is low with minimally invasive ablation?**

Pech: Today, RAS mutation status already determines an unfavorable subgroup of colorectal cancer patients. I believe that local tumor ablation should be considered earlier and more intensely in mutants than in wild-type patients. In the future, better interdisciplinary cooperation is a must. Local ablation should always be considered as an additional option that may prolong the time to switch off the chemotherapy line, i.e. to induce the next chemotherapy line after progression. According to the clone selection model, these patients are specifically represented in the 'mixed response group' – ablation removes clones not sensitive to the current chemotherapy line. Again, a mathematical model may support this hypothesis: Norton and Simon (in the 1970s!) proved that chemotherapy results in a rate of regression in tumor volume that is proportional to the rate of growth for an unperturbed tumor of that size. The drug effect is not just the concentration of pharmacokinetics multiplied by time, because the relationship between drug dose level and anticancer effect is not always linear. Finally, the smaller a tumor, the more likely is chemoresistance due to the likelihood of a surviving resistant clone fraction: a case for local ablation.

In brief: Prospective studies are desperately needed to assess what truly happens when local treatments imply selection pressure on tumor cells and the resulting mutational status. Cytoreduction may be underrated and a perhaps forgotten cornerstone of oncological treatment concepts in solid gastrointestinal or other tumors.

Bruns: In the event of oligometastasis in stage IV colorectal cancer, it is essentially important to know whether these multiple metastases are prevalent synchronously or metachronously with the primary tumor. This raises the fundamental question whether the metastatic genotype of the different metastasis has already been defined in the primary tumor, or whether the different localizations are due to metastasis from other metastases. Also, the issue arises to what extent certain known patterns of mutations or combinations thereof (NRAS, KRAS, BRAF, PTEN, APC, TP53, PIK3CA) are associated with a particular form of oligometastasis. Prognostic or predictive marker profiles that foresee oligometastasis are not yet known. Oligometastasis is biologically not yet registered, and therefore cannot necessarily be regarded as prognostically unfavorable. Similar to monometastatic patients, subgroups of patients with oligometastasis in stage IV colorectal cancer show favorable courses, of which the underlying tumor biology is not yet understood. At present, these biologically favorable groups of oligometastasis can be identified by clinical parameters such as response to therapy and disease-/progression-free survival and imaging features (tumor size decrease by RECIST (Response Evaluation Criteria In Solid Tumors)). These benefit from a surgical treatment in the sense of increasing deepness of response and thereby favor an overall survival.

In synchronous oligometastasis, which affects most commonly lymph nodes, liver and/or lungs in colorectal carcinoma, aside from the question of the treatment type there is also the question of the treatment sequence. A clear recommendation regarding the treatment sequence in synchronous liver and lung metastasis of a sigmoid carcinoma, for instance, does not exist. Thus, the sequence of treatment is dependent on several factors, and is therefore different for individual subgroups of patients with synchronous liver and lung metastasis of colorectal carcinoma. Major influences of the treatment sequence are:

– Asymptomatic or symptomatic (bleeding, stenosis, ileus) primary;
– resectable liver metastases or primary nonresectable liver metastases, however, after downsizing potentially resectable;
– remaining liver tissue (hypertrophy induction required) after resection sufficient or not sufficient;
– comorbidity present or not present (cardiopulmonary, hepatotoxic renal, metabolic).

This consequently results in the following questions regarding the treatment sequence:

– Does the resection of the primary make oncological sense? If so, when will the surgery in the treatment sequence take place? Should a bowel anastomosis be done? Should a colostomy be created additionally/exclusively?
– When is resection of the liver metastases done: liver-first or liver-second?
– Is hypertrophy induction required (portal vein embolization (PVE), Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS))?
– Can liver metastasis only be approached surgically in terms of a two-stage procedure?
– When is the surgery of lung metastases scheduled?
– Is there chemotherapy between the surgical procedures? If so, which one and for how long?
– Should antibodies be administered additionally to systemic therapy? If yes, which one and for how long?
– Should locally ablative procedures be considered solely or in combination with surgical and systemic therapy?

The German S3 guidelines for colorectal cancer recommend surgical resection of isolated resectable liver and lung metastases up to the recommendation that even primarily nonresectable isolated liver metastases can be resected secondarily. If the objective of therapy is the induction of remission with secondary resection of liver metastases, then the most effective in each case available systemic therapy should be applied (intensified therapy). It is important to regularly evaluate a possible secondary resectability after induction of remission.

Recent prospective studies should at least clarify the treatment sequence for synchronous liver metastasis in stage IV colorectal cancer (synchronous study). The surgical treatment of resectable lung metastases presently seems to be of secondary importance in liver-dominant metastasis type in the surgical treatment sequence.

Wust: In principle, radiotherapeutic treatments are utilized when a malignant disease spreads out only locally, regionally, or is limited to very few foci. Based on the tumor biology, we can find such behavior in colorectal cancer, renal cell carcinoma, and malignant melanoma, but occasionally also in breast cancer, non-small cell lung cancer, prostate cancer, sarcomas, and rarely in pancreatic cancer.

Depending on the localization and expansion of the solitary or oligotop manifestation, brachytherapy (e.g. liver metastases), radiosurgery (CyberKnife, high single doses), stereotaxis (Novalis, fractionated), and intensity-modulated radiation therapy (IMRT), particularly tomotherapy and RapidArc (in complex regional expansion), are taken into consideration.

In smaller lesions local control can be achieved more likely. Beyond a tumor expansion of 4–5 cm it is quite difficult to

apply a sufficiently high, biologically effective dose of 70–90 Gy in the whole tumor.

In an extensive target area more fractionation is necessary. The modern SIB (simultaneous integrated boost) concept allows to attain a sufficiently high dose of 70 Gy (conventionally fractionated) even in multiple scattered tumors without burdening the normal tissue in between too much.

Due to the improvement of systemic therapy, local therapies gain a higher value, which seems surprising at first glance. After an aggressive, in a microscopic area effective, systemic therapy, an oligotop pattern of residual tissue may remain. Positron emission tomography (PET) is increasingly utilized to localize this residual tissue. The remaining (oligotop) tumor manifestations are eradicated with a so-called consolidating radiation. It is already an established approach in Hodgkin's disease, non-Hodgkin lymphomas, and non-small cell lung cancer. With increasingly effective systemic therapies there is hope that this strategy will be available for other tumor entities (e.g. breast and prostate cancer) as well.

On the other hand, improved local and regional radiation therapies (e.g. tomotherapy) will be utilized in cases which were previously considered incurable due to probable metastatic spread. In these cases, an effective maintenance therapy is necessary to keep disseminated microscopic lesions under control. An interesting example is prostate cancer in combination with antiandrogens.

Question 5: Professor Dietrich, through the eyes of the gastroenterologist: What are the ablation techniques you see at the front line today?

Dietrich: I favor ultrasound guidance. Ultrasound-guided tissue ablation is technically feasible in all cases where ultrasound or other imaging methods can define a safe access route to the lesion – that of course gives it some limitation to liver or renal tumors. The maximum number of tumors that can be reasonably ablated is not clearly defined but ranges from 3 to 5 at most centers. There is no established standard for the maximum tumor size that can be ablated but typically a limitation to 4–5 cm applies if thermal techniques are used. Tumors larger than 2 cm may require multi-needle ablation depending on the ablation device. A safety margin of at least 5–10 mm will help to minimize local recurrences. New techniques such as the simultaneous or consecutive use of multiple ablation probes as well as stereotactically guided RFA can successfully treat tumors of up to 10 cm in diameter. Giant tumor ablation has been performed using (repeated) ethanol injections under general anesthesia in some centers but data are lacking and it remains questionable whether the distribution of the agent is reliable for safe local tumor control. Attention must be paid to vulnerable structures adjacent to the tumor and the ablation zone. Thermally induced bowel perforation is a complication that has been described in liver tumor ablation by RFA. The stomach, gall bladder, and diaphragm are less thermosensitive, and tumors in proximity to these structures can generally be ablated with somewhat less difficulty. The ultrasound-guided intraperitoneal injection of glucose solution to separate hollow organs from the liver surface before ablation is an established method of avoiding thermal injury. RFA of lesions that border directly on central bile ducts is contraindicated due to the risk of thermal injury. Close proximity to large hepatic vessels is problematic because these vessels are efficient heat eliminators, potentially leading to incomplete ablation or local recurrence. This problem can be solved by the concomitant, transient embolization of arterial branches supplying the liver, causing a temporary reduction in blood flow. In summary, RFA is the most widely used technique today for thermal tumor ablation. Microwave ablation may be competitive and is performed with increasing numbers – comparative data, however, is missing to date. With respect to image guidance, advantages of ultrasonography are its real-time capability, its high spatial resolution, and its widespread availability. Ultrasound has proven particularly advantageous in the puncture of subdiaphragmatic liver lesions as it can safely avoid accidental puncture of the pleura and lung. Tumor margins are better detected by contrast-enhanced ultrasound (CEUS) than unenhanced ultrasound.

General Comment

Ricke: I would like to add a general comment closing this discussion. What we have learned is that the oncological rationale in the treatment of solid gastrointestinal tumors is undergoing sincere changes. Clone selection processes specifically in regard to targeted molecules as well as the concept of oligometastatic versus politopic disease are gaining an increasing interest. In addition, there is great innovative potential from the technical perspective minimizing access and local trauma during local tumor treatments. It seems rather uninteresting who is performing a given procedure – be it surgeons, radiologists, gastroenterologists, radiation oncologists, or others; decisive is solely the available tool box at any given institution when treating the patient. A distinct tool box also allows for combinations of treatments, such – as we can see today – as with portal vein or radioembolization to induce liver hypertrophy, the latter enabling hepatectomies and so on. Personally, I have no doubt that radiation therapy will soon deliver more and very positive surprises: radiation therapy can be planned and performed with unmatched precision, sparing adjacent risk organs and overcoming heat sink effects of thermal approaches such as RFA. Stereotactic irradiation without a doubt is an extremely elegant method with typically no major trauma or patient discomfort. However, its percutaneous application mode induces a dose bath, leaving it unbeaten only in solitary lesions, limited tumor size, and in situations where repetitive approaches are unlikely. In multiple

or very large lesions, internal irradiation through catheters inserted in the tumor – a method established 100 years ago – delivers very high radiation doses with extreme precision when modern imaging techniques such as computed tomography (CT) or magnetic resonance (MR) fluoroscopy are used. Details on both techniques can be found in the remarkable article by Mohnike and Hass [3] in this issue. To illustrate the future potential of these techniques: At the EASL (European Association for the Study of the Liver) 2013, Mohnike presented a study randomizing CT brachytherapy against chemoembolization in patients with hepatocellular carcinoma (HCC) [4]. In the subgroup of BCLC B patients, where transarterial chemoembolization (TACE) is the established treatment modality, brachytherapy improved time-to-progression and overall survival with far less interventions necessary than in the TACE group. I am convinced that we will see further positive outcomes in future clinical study formats of local tumor ablation of gastrointestinal tumors!

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