Viral Hepatitis and Its Complications: Management of Hepatocellular Carcinoma

Chair: Wolf. O. Bechstein^a

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Question 1: Regarding early detection of hepatocellular carcinoma (HCC), do your screening programs differ between patients with viral hepatitis as underlying disease from those with other causes of cirrhosis?

Galle: No, we perform ultrasound and alfa-fetoprotein every 6 months, irrespective of etiology. The pivotal question is whether to include patients in screening/surveillance programs or not, and in many patients this requires an individual decision. However, if surveillance is performed, 6-month intervals are superior to 12-month intervals but not better than 3-month intervals.

Nashan: Contrast-enhanced ultrasound (CEUS) is the typical choice for screening patients with any type of cirrhosis for HCC on a regular basis. According to the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver guidelines, which favor this approach, the sensitivity is between 65 and 80% and the specificity is around 90%.

Pratschke: No, the screening programs do not differ.

Ricke: From the radiologist's point of view, no differences apply. Screening sonography supplemented by i.v. contrast application is performed in any cirrhotic patient at regular intervals. In case of suspicious findings, the next imaging modality is added; the standard would normally be hepatobiliary magnetic resonance imaging (MRI).

Vogl: Patients with chronic viral hepatitis, especially hepatitis type C, are checked in a regular follow-up using ultrasound, CEUS,

and – in the high-risk group – also contrast-enhanced MRI in 6-month intervals. In patients with chronic viral hepatitis, the clinical program is more intense and detailed in comparison to other underlying liver diseases. We perform an intensive screening program in patients with hemochromatosis.

Question 2: Do you attempt to obtain a histological diagnosis of HCC before treatment, and if so, why?

Galle: We obtain biopsies or histology after resection in >90% of the patients. Availability of tissue is the only way to stratify HCC patients into subgroups in order to optimize treatment outcome.

Nashan: Imaging using ultrasound, computed tomography (CT), or MRI in lesions smaller than 2 cm or CT or MRI in lesions larger than 2 cm alone reflects the current standard. Hence, a histological diagnosis is not state of the art but can be necessary in unclear cases.

Pratschke: No, we do not obtain a biopsy; we rely on CT and MRI.

Ricke: Generally speaking, the non-invasive imaging criteria provide sufficient specificity to also rely on them for therapeutic decisions – as proven by their acceptance in multiple guidelines. We always promote biopsy in case of lesions that are not 'perfectly typical' with clear wash-in and wash-out, bearing in mind that specifically lesions early in the carcinogenesis cycle, such as dysplastic nodules, yield a substantial sampling error potential – up to 35% of

HCC islets found in high-grade dysplastic nodules in a study from the Bologna group (Bolondi et al.). The second reason to be quite aggressive in performing biopsies often is that almost all our patients are study subjects; for analyses of prognostic markers or identification of histopathological subgroups, the acquisition of tissue is absolutely essential.

Vogl: In Frankfurt, patients with suspected HCC regularly undergo a histopathological diagnosis using ultrasound-, CT-, or MRI-guided percutaneous biopsies, especially for the liver transplantation program. Whenever technically possible, we try to obtain histological proof of HCC, especially in patients who are on the waiting list for transplantation or for patients who participate in clinical and pharmaceutical studies.

In patients with severe coagulation disorders or different clinical problems, we avoid percutaneous or vascular biopsy of the tumors and rely on imaging, especially regarding the different HCC imaging criteria.

Question 3: In stratifying patients for treatment of HCC, do you strictly follow the Barcelona Carcinoma of the Liver Classification (BCLC) or do you make exceptions? In which cases would you diverge from this algorithm?

Galle: Real-life assessment, e.g. in the BRIDGE trial, demonstrates a significant deviation from BCLC-based treatment recommendations all over the world. Selective internal radiation therapy (SIRT) instead of transarterial chemoembolization (TACE) as well as TACE in BCLC-C patients with liver-dominant disease are examples of such exceptions which account for 30–50% of all HCC patients as a result of individualized decisions in multidisciplinary teams.

Nashan: We follow the BCLC classification but there is always room for individual decisions based on findings and consensus within the tumor board.

Pratschke: In general, we follow the BCLC. After assessing liver function, we perform an increasing number of tumor resections laparoscopically if functional tests are proving sufficient liver function.

Ricke: BCLC is extremely static. Specifically the BCLC-B group, ranging from a single, well encapsulated large lesion to numerous, infiltrative lesions, or from Child-Pugh 7–9 points, must certainly be stratified into further subgroups – to identify patients likely to benefit from resection or extended local ablation such as through stereotactic body radiation therapy (SBRT) or CT-guided brachytherapy, or from systemic or no treatment rather than interventional methods. For Y90-radioembolization, clear evidence must still be awaited; I expect that a combination concept of Y90-radioembolization plus sorafenib may show benefit in BCLC-C pa-

tients, such as tested in Magdeburg's SORAMIC trial with results expected in 2017. Additionally, we are convinced that TACE truly is better than Y90 in 'early' BCLC-B, given the very limited data at hand. The published response rates are always higher for Y90-radioembolization as compared to TACE, and the few studies comparing both techniques with similar overall survival are single-center cohorts lumping together a limited number of patients demonstrating all tumor stages from BCLC-A through to D (such as the Salem publication in *Gastroenterology* from 2011).

Vogl: The BCLC has been validated in different settings, and it provides recommendations for the treatment of all stages of HCC. The treatment of patients in our hospital is based on the BCLC classification, too. In some cases we have to diverge from the above-mentioned algorithm, especially if a patient prefers ablation instead of surgery.

Another case where we diverge from the BCLC is the treatment of patients with BCLC stage D. Those patients possibly receive a combination therapy of TACE and systemic sorafenib according to a study protocol.

Question 4: In your experience, which are the most important contraindications against interventional locoregional treatments of HCC (transarterial embolization (TAE), TACE, and SIRT)?

Galle: Poor liver function (bilirubin ≥ 3) and main-trunk portal vein thrombosis are the most relevant contraindications.

Nashan: The choice of therapy is influenced by factors such as extent of tumor and severity of underlying liver dysfunction as well as availability of resources and expertise. The most important contraindications against interventional treatment are either anatomical location (close proximity to vessels or capsule) or a combination of BCLC-C or -D in combination with ECOG scores > 2 . Regarding SIRT, we do have experience in very well selected individual cases.

Pratschke: Ascites, massive portal hypertension, location of the tumor close to vessels, curative therapeutic approach.

Ricke: I believe an important and sometimes underestimated aspect is the clinical presentation and performance status of the patient. Locoregional treatments may be aggressive in regard to liver function even if performed selectively; however, survival data from a median of 30 up to 42 months for TACE in BCLC-B patients can only be reached with well compensated liver function and a generally good health status. Patients with compromised liver function and performance status should be examined quite carefully if appropriate for locoregional treatment – or if they would not benefit more from systemic treatment. It seems (but has not been validated sufficiently to be a part of the guidelines) that Y90 may be more favorable than sorafenib treatment in terms of toxicity specifically in the elderly or in patients with comorbidities (e.g. published by

Gramenzi in 2015). We will only know after the according trial (e.g. SARAH in France) has published the head-to-head results between Y90 and sorafenib whether there also is a survival difference between both treatment options.

Vogl: Contraindications for transarterial locoregional treatments of HCC are:

- Child-Pugh C with high serum total bilirubin level (>2.5 mg/dl) and poor hepatic synthesis (albumin level < 2.0 mg/dl in serum).
- Patients with $>70\%$ hepatic involvement of the tumor, since treating such patients might impair the remaining liver function and lead to liver failure.
- Complete thrombosis of the main portal vein and portal invasion.
- Extrahepatic metastases.
- Inadequate performance status as judged by an ECOG > 1 .
- Inadequate blood coagulation (prothrombin time > 6 s, thrombocytopenia ($\leq 30,000/\mu\text{l}$)).

In my experience, the most important contraindications against interventional locoregional treatments of HCC are: systemic progression of the disease including lung and/or brain metastases; major failure of the liver with increased liver values; vascular impairment, especially thrombosis of the hepatic arteries or arterial dissection due to the previous therapies. Portal vein thrombosis is in my opinion rather a relative contraindication for those patients who can be also successfully treated with TAE.

Question 5: Is there a place for neoadjuvant treatment before resection of HCC?

Galle: Scientific evidence for such an approach is lacking, and systemic therapy does not typically yield meaningful responses and subsequent resectability of previously unresectable tumors. Nevertheless, in individual patients with very good liver function and unilobar disease, SIRT treatment resulting in tumor control and contralateral hypertrophy occasionally improves resectability.

Nashan: Well, is TACE so to say not already some type of neoadjuvant therapy? Even SIRT is used in selected rare cases as neoadjuvant therapy prior to resection. From that point of view, we are already performing a kind of neoadjuvant therapy approach for either resection or transplantation where we call it bridging.

Pratschke: Not with the available substances.

Ricke: No, at least not as a standard approach. Maybe in non-cirrhotic patients but certainly not in cirrhotics with portal hypertension or a MELD score > 9 .

Vogl: In our opinion, the presurgical performance of transarterial angiography/TAE/TACE and portal vein embolization helps first of all to identify the location of the tumor with lipiodol mark-

ing. Secondly, if a possible downsizing can be verified in the imaging, those patients can become possible candidates for surgery or for thermal ablation.

Question 6: Is there a place for adjuvant treatment after resection of HCC (including antiviral treatment)?

Galle: The SPACE trial clearly provided a benefit for sorafenib-treated patients in an adjuvant setting after TACE with drug-eluting beads (DEBDOX).

Nashan: Talking about chemotherapy, adjuvant treatment after resection warrants evidence by studies before recommendation. Antiviral treatment for hepatitis B virus is state of the art, and given the success story with antiviral treatment for hepatitis C virus, this therapy will soon be state of the art as well.

Pratschke: In viral infections, there is a clear indication for the eradication of the virus; rapamycin as an adjuvant treatment can be considered. Otherwise, there are no sufficient options.

Vogl: If surgery is performed as an R0 resection or ablation as an A0 ablation, I do not see an indication for adjuvant treatment. Adjuvant interferon alfa-2b has failed in randomized trials and did not reduce the local recurrence rate. However, randomized trials evaluating new molecular drugs are on the way. Currently, TACE or TAE do not play a role as strictly adjuvant treatment.

Question 7: Generally, so-called Milan criteria are used as selection criteria for liver transplantation – are these too narrow or do they serve their purpose well?

Galle: The so-called Metroticket discussion clearly showed that the extension of the Milan criteria is coming at a prize: The further you go, the higher the prize; extension results in higher recurrence rates. Organ shortage further prevents this. However, there are data suggesting that not the initial size but rather the dynamic development of the tumor is predictive.

Nashan: There is a long debate about the evidence of the Milan criteria as a criterion for standard exceptions in liver allocation for transplantation. Currently, we have specified the Milan criteria using the TNM classification for liver allocation in transplantation. As a next step, a national study to evaluate the benefit of extending the Milan criteria to the University of California, San Francisco (UCSF) criteria is under way, and we will see if a change in classification to a larger tumor mass will be the solution. In this study, an assessment of tumor biomarkers is planned as well since the truth will probably be not only size but rather tumor biology in combination with size.

Pratschke: They are too narrow. A classification which takes into account the biology of the tumor should be introduced.

Vogl: We strictly use the Milan criteria for the diagnosis or evaluation of patients with HCC and discuss the data in our multidisciplinary liver cancer and transplantation board. One study from 2007 showed some improved surgical data in HCC beyond Milan but with UCSF criteria. However, we follow the Milan criteria.

The Milan criteria are very useful and helpful as standardized selection criteria for patients with HCC on a waiting list for liver transplantation.

Changing or expanding the Milan criteria is an attempt to extend the preexisting protocol for patients with HCC on a waiting list for liver transplantation. However, data show that there is no significant difference in the patient survival rate and tumor recurrence-free rate from those patients that followed the Milan criteria.

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