Liver Therapies

Despite progress with respect to detection, diagnosis, surveillance and treatment, hepatocellular carcinoma is the third leading cause of cancer deaths. Presentations outlined trends and accomplishments, identified remaining hurdles, and highlighted the myriad ways interventional radiology contributes to the increasingly multidisciplinary fight against liver cancer.

Early-stage HCC

Prof. Valérie Paradis (Clichy/FR) addressed the **pathology of early HCC**, focusing on tumours smaller than 2 cm. Advances in imaging techniques and screening protocols for high-risk populations have led to better detection of small nodules, but differentiating between pre-malignant nodules, such as high-grade dysplastic nodules, and early HCC, and between early and progressed HCC, remains challenging. Biopsies can be particularly helpful, both for differential diagnoses and to provide prognostic indicators, and cooperation between pathologists and radiologists is essential to properly analyse both macro- and microscopic tumour patterns.

Dr. Christoph Zech (Basel/CH) tackled **imaging of early HCC**. Where patients suffer from either cirrhosis or longstanding viral hepatitis, and imaging shows hyper-vascularity and washout, imaging can suffice. MRI is especially useful, thanks to diffusion-weighted imaging and the use of tissue-specific contrast media. However, vascular criteria have limitations, and imaging alone does not always resolve the diagnosis, meaning a biopsy is necessary. Once early HCC is diagnosed, accurate staging is crucial for treatment purposes, particularly with cure a possibility. Dr. Zech noted that all imaging technologies can have difficulties with lesions smaller than 1 cm, and identified MRI with hepatobiliary contrast imaging as a significantly superior technique.

Moderators Eveline Boucher and José Ignacio Bilbao hosted an informative session on early-stage HCC




Dr. Nisar Malek (Tübingen/DE) discussed **why and how to biopsy**. Where imaging is not characteristic, and a tumour is smaller than 2 cm, a biopsy should be performed (with tumours larger than 2 cm, second imaging suffices). Biopsies can also help estimate the risk of HCC formation in cirrhotic livers, and, with small HCC, provide additional genetic information that assists physicians in making correct diagnoses. Moreover, tissue analysis can help predict recurrence following curative treatment, and should become a standard part of treatment. Biopsies can also facilitate predicting a patient's response to treatment, and could play an important role in guiding future, more individualised care.

Dr. Pietro Majno (Geneva/CH) addressed **transplantation waiting lists**. The medical community has expressed concern about drop-outs, with many urging that transplants be performed sooner, or bridging treatments used. Dr. Majno maintained that recurrence is a bigger problem, and that simply observing patients during the wait is an often-overlooked option that makes sense in certain cases. While bridging treatments – limited to TACE or RFA for early HCC – have shown to be effective for patients facing waiting times between 6 and 18 months, he questioned their value for T2 patients who have to wait less than six months, as well as for T1 patients. Deciding when to delist patients is an important question, and better data is necessary to answer it.

Prof. Riccardo Lencioni (Pisa/IT) reviewed the **evidence on resection vs. ablation** for early HCC. Randomised controlled trials so far preclude clear comparisons, but studies on very small tumours (average of < 2.5 cm) have demonstrated that the two are equally effective. For patients who qualify for resection but suffer from a solitary, small tumour, ablation and resection are both good curative options (with tumour location a vital parameter); and for patients precluded from resection, ablation is the best option, though response rates will not be as high where tumours reach 5 cm. However, individual discussions of cases remain important. Furthermore, truly improving long-term outcomes requires tackling recurrence, and research on novel drugs and molecular-targeted therapies in adjuvant settings, following resection or ablation, should be a priority.

Intermediate-stage HCC

Dr. Riad Salem (Chicago, IL/US) assessed **the BCLC and HKLC systems for HCC**. The BCLC has been widely used for clinical trials, and recommended by Western scientific societies for clinical practice. However, it has been criticised for oversimplifying HCC and for being too conservative. The Hong Kong staging system refined stratification by tumour number, size and PVT; introduced the concept of locally advanced tumours; and created a unique stage for certain transplantable early HCC. It also reflects a more aggressive approach, emphasising surgery in intermediate and advanced disease and endorsing RFA for lesions larger than 5 cm. However, the system requires further validation. This necessitates adapting local practice, which is controversial.

The Video Learning Session took the audience through various liver cancer procedures step by step.

Dr. Patrick Chevallier (Nice/FR) addressed the role of **ablation in intermediate HCC**. With monopolar RFA linked to high recurrence, modifications are clearly necessary. Options include increasing the ablation area, but the few studies available indicate that even a large security margin around the main tumour may not prevent recurrence in case of local invasion. Combining RFA with another therapy is also an option. Under certain circumstances, combining TACE and RFA can be beneficial for patients with either a single lesion of 3-5 cm or multiple within the Milan criteria. However, more solid scientific proof is needed. In the meantime, identifying patients beyond BCLC A who might benefit from ablation will remain more of an art than a science.

Prof. Thomas Helmberger (Munich/DE) scrutinised **drug-eluting beads versus conventional TACE**. Current practice focuses on one liquid agent (Lipiodol) and several particulate agents, both bland and drug-eluting. Drug-eluting beads entail a low drug concentration in plasma and a higher or longer concentration in the tumour. Vascular complications are rare, but non-vascular complications are quite common. Research suggests these occur somewhat less frequently with DEB-TACE. While TACE has evolved, and DEB-TACE may be superior to the classic approach, demonstrating statistically significant improvements in survival rates remains elusive, and there is no consensus on the optimal technique.

Dr. Eveline Boucher (Rennes/FR) addressed radioembolisation for **intermediate HCC**. Dividing BCLC stage B into four sub-categories based on CPT score, liver status and tumour load, she endorsed the therapy for BCLC B3 patients (with impaired liver function) and BCLC B2 cases (especially with large and multifocal tumours), and as an alternative to resection for BCLC B1 patients who do not qualify for surgery for general reasons. She noted that radioembolisation can be performed in an outpatient setting, and can be adapted to the tumour load, but acknowledged that TARE is new, entailing a high learning curve and risk of adverse events; that it requires true cooperation between units; and that it is expensive.



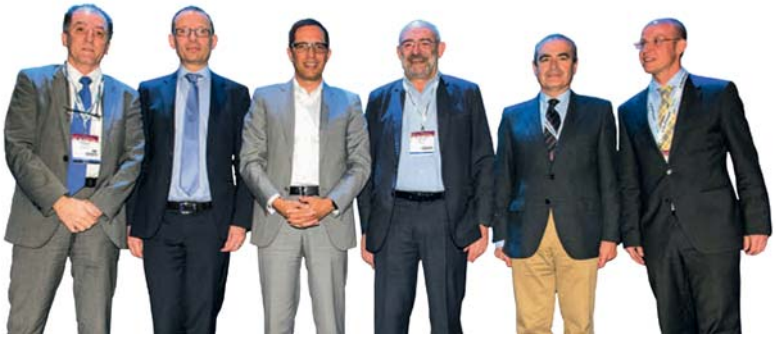

Dr. Rodolphe Anty (Nice/FR) outlined the current evidence regarding **systemic therapy in intermediate HCC**, noting that the heterogeneity of tumours and variety in molecular pathways add considerable complexity. Sorafenib is effective in BCLC C and B patients, and, in practice, is offered to patients who do not qualify for TACE, or for whom TACE fails. Recent efforts focus on using Sorafenib to optimise TACE, but meta-analyses of this approach have yielded contradictory results, and results of a new randomised Phase III study comparing Sorafenib and DEB-TACE to DEB-TACE alone are pending. Finally, at this point, no clear evidence supports using Sorafenib as adjuvant after either resection or ablation.

Colorectal liver metastases

In a joint session with ESMO, Dr. Marc Peeters (Edegem/BE) stated that the ultimate goal of **personalised medicine in oncology** is sufficiently defining the disease to enable identifying and treating only those patients most likely to respond. It focuses on using biomarkers to help predict treatment safety and/or outcome efficacy. Technological advances are also leading to the use of gene panels, but the medical community needs to determine whether the information suffices to justify clinical changes. Reorganisation is also needed as pathologists switch from routine pathology to molecular pathology. In addition, personalised medicine involves more multidisciplinary teams, which can be challenging. Finally, managing the costs of all the new information and technology is also crucial.

Prof. Jean-Yves Douillard (St. Herblaim/FR) indicated that most CRCLM patients are fit to receive **systemic therapy**, but that this decision should be made by a multidisciplinary team. Available cytotoxic agents include three main groups (Fluoropyrimidines, Irinotecan and Oxaliplatin), as well as the rarely-used Raltitrexed. It is also possible to add two categories of biological agents to chemotherapy (anti-angiogenesis and anti-EGFR). For patients with resectable metastases, perioperative chemotherapy provides modest, non-significant improvement, but for patients with potentially resectable metastases, downsizing by way of chemotherapy does result in 5-year survival rates similar to initially resectable patients. However, most patients encountered are unresectable, and chemotherapy is used to extend survival, control symptoms and preserve quality of life.

Prof. Michel Ducreux (Villejuif/FR) outlined the rationale and indications for **hepatic intra-arterial delivery of chemotherapy in CRCLM,** which places a high level of concentration into the metastases without resulting in too much systemic spread, preventing toxicity. Several drugs can be used, including 5-fluorouracil and a potential game-changer, Oxaliplatin. Intravenous administration will always remain simpler. Also, the literature on the arterial approach has not shown improved overall survival. However, Oxaliplatin, a new drug, is promising, even in patients resistant to intra-venous administration of the drug. Combining HAI of Oxaliplatin with chemotherapy (cetuximab) has also yielded good results. In patients who undergo resection, adjuvant administration of HAI after surgery shows positive results in terms of recurrence-free survival, but again only with Oxaliplatin. Efforts to produce Phase III trial results are underway.



The speakers and moderators from the Joint Session with ESMO

Prof. José Ignacio Bilbao (Pamplona/ES) detailed study results on **radioembolisation in CRCLM**, including the SIRFLOX study, which compares SIRT with FOLFOX to FOLFOX alone as a first-line treatment for non-resectable CRCLM. Initial results from March 2015 show no statistically significant improvement in progression-free survival at any site. However, adding SIR-Spheres Y-90 resin microspheres to a chemotherapy regimen did show such a statistically significant improvement in PFS in the liver compared to chemotherapy alone. Two other studies, FOXFIRE and FORXFIREGlobal, should shed further light on the issue, but results will not be available for another year.

Dr. Christoph Zech (Basel/CH) noted that the growth in therapeutic options has rendered **assessing tumour response after TACE/SIRT** more complicated. Although traditional approaches (the RECIST criteria and volumetry) still dominate, new functional approaches show promise. Perfusion MRI remains insufficiently standardised, but PET-CT is faring better, and could be very useful in gauging overall survival based on early response. However, it is vital for physicians who review follow-up examinations to be aware of the possible variety in imaging findings, including an increase in size and other unexpected findings that must be correctly interpreted.



Managing complications

Dr. Shaun Samuels (Miami, FL/US) explained that major complications from **TACE** include hepatic failure, hepatic abscess/biloma, cholecystitis and death, then outlined three situations in which he and other interventional radiologists encountered difficulties. His advice for preventing complications included avoiding a "macho mentality" by refraining from pushing the limits of one's therapy; letting a surgeon get involved where necessary; with respect to HCC, being aware of the variety in feeding vessels; and consulting colleagues.

Dr. Patrick Chevallier (Nice/FR) discussed digestive complications following **RFA** in the liver. Colonic perforation, while infrequent, is always associated with morbidity, as well as death in up to 40%. Typically discovered 5-8 days after RFA, it usually requires surgery. It can generally be prevented by colonic insulation; contraindicating patients is recommended where colonic protection is not possible. Gastric perforation is another complication; its frequency is unknown and symptoms vary. Associated with severe morbidity, it can and should be prevented through heat insulation.

Prof. Carmen Ayuso (Barcelona/ES) also addressed complications following **ablation**, including bleeding into the liver, the most common direct complication; portal vein thrombosis, caused by heat damage; liver infarction; extra-hepatic organ injuries; and liver failure, which is most commonly encountered in cases involving prior hepatectomy or with cirrhotic patients. Prof. Ayuso also summarised the results of a Japanese survey of over 13,000 patients, reporting a mortality rate of 0.038%, and major complications with 3.54% of nodules.

Dr. Andreas Mahnken (Marburg/DE) focused on complications following **radioembolisation**, asserting that post-radioembolisation syndrome, a common adverse event, should be considered a side-effect. Other risks include hepatic dysfunction, hepatic fibrosis and portal hypertension, radiation choleystitis and radiation-induced cholangitis. Dr. Mahnken outlined several challenges encountered, including duodenal ulceration, which, after radioembolisation, can only be successfully treated with proton pump inhibitors in about 50% of patients; other anti-inflammatory treatments show promise, but currently remain experimental.

Other sessions

A multidisciplinary tumour board brought together a hepatologist, interventional radiologists and a surgeon to analyse five cases involving HCC. The experts agreed almost entirely on how to proceed, but were able to offer unique insights based on their various perspectives.

Finally, a video-learning session also focused on liver treatments, with experienced physicians explaining how they perform various percutaneous procedures, covering liver ablation and venous occlusion, combined cTACE and ablation, DEB-TACE, Y-90 and PVE.

*Presentations are available at **www.esir.org***