New Horizons

Throughout the meeting, presentations detailed the current status of myriad ablation procedures, introduced new areas of application, and outlined various recent insights in molecular oncology, providing an intriguing glimpse into the future of oncological care.

Ablation: current status and future horizons

Multiple ablative modalities are available, Dr. Brad Wood (Bethesda, MD/US) noted, but **radiofrequency ablation** entails several benefits, including that it is time-tested, with more long-term data available. Results are comparable to resection for small (< 5 cm) HCC in overall and disease-free survival. In addition, RFA is predictable at the tip, cauterises better than cryoablation, and its "slow cooking" can be advantageous. Promising developments include combination therapies (with TACE, XRT and drugs), and advancements in immunotherapy, with an "RFA vaccine" holding the potential to dramatically change cancer care. The modality is also being extended to new organs, including the prostate, pancreas and breast.

Prof. Nahum Goldberg (Jerusalem/IL) provided a detailed update on **electroporation**. The drawbacks of standard techniques used to treat small, solid tumours (such as RF, MW and cryoablation) include heat-sink effects and potential damage to adjacent structures. Electroporation entails no heat-sink effect and has limited impact on the bile duct. However, it requires general anaesthesia and cardiac monitoring. Predictability is also an issue: more research is clearly required. However, where other techniques are not suitable, IRE shows potential for use in previously untreatable disease, especially pancreatic cancer and liver tumours in difficult locations.

Prof. Philippe Pereira (Heilbronn/DE) addressed **microwave ablation**. Devices now feature high-power and internally cooled antennae, as well as thermal, field and wavelength controls. For liver tumours smaller than 3 cm, RFA and MWA produce similar results. Research also indicates that local recurrence rates for HCC and colorectal cancer hepatic metastases are significantly better with microwaves. MW also entails less heat-sink effect, less perfusion-mediated cooling, and faster heat generation, which allows better treatment of liver tumours near large vessels. In addition, it is a good option for lung tumours because of the limited heat conductivity of pulmonary tissue.




Dr. Irene Mindjuk (Dachau/DE) discussed **HIFU**. MR-guidance offers exact tumour location, the ability to avoid critical structures thanks to visualisation of the treatment zone, and real-time thermometry for therapy control. US-guidance is more frequently used and entails lower costs, but is highly operator-dependent. Clinical applications have expanded. Uterine fibroids are one of the best-developed indications, and technological improvements have reduced skin burns. In Europe, HIFU is also approved as a first-line treatment for bone metastases, primary benign and malignant bone tumours, multiple myeloma and facet joint syndrome. The evidence on its efficacy for prostate cancer is still limited. Applications in neurosurgery are promising. However, more RCTs are needed.

Dr. David Breen (Southampton/UK) views **cryoablation** as underused, especially in Europe. Many centres resist cryo because it involves large Argon and Helium tanks, but companies are predicting "tank-less" cryoablation by late 2016. Other efforts include producing thinner probes, which now have shaft insulation to prevent skin burns. Cryo's main benefit is cryo-lesion conspicuity. In addition, the ablation zone appears to fade faster than with RFA. Cryoablation shows particular strength in bone tumour ablation, pain palliation for malignant bone disease, adrenal ablation, and chest wall disease. There is some debate as to its role in focal prostatic disease.

Dr. Martin den Brok (Nijmegen/NL) discussed **combining immunomodulation with ablation**. Immunologists are exploring an *in vivo* dendritic cell (DC) vaccine, which requires both antigen-loading of DC *in vivo* and maturation of DC *in vivo*. The former is done via in situ tumour destruction. Several ablation techniques, especially cryoablation, have been investigated. Researchers are now turning towards HIFU; mechanical ablation shows particular promise, completely destroying cell structures. In terms of DC maturation, combining ablation with CpG, a synthetic nucleotide sequence, greatly benefits immunity. It has become clear that even greater immunity results when ablation is combined with immune stimulating complexes (ISCOMs); the researchers now plan to test combining CpG and ISCOMs.

Ablation: expanding the boundaries

Dr. Jung Hwan Baek (Seoul/KR) addressed RFA for **benign thyroid nodules**. Korean guidelines identify three indications: symptomatic problems, cosmetic problems, or hyper-functioning nodules related to thyrotoxicosis. The procedure involves local anaesthesia, and guidelines recommend two techniques (the trans-isthmic approach and the moving-shot technique). Clinical outcomes for patients with symptomatic problems entail a volume reduction of around 50% at one month, of 90% at one year, and the effect was maintained throughout the 4-year follow-up. Complications include voice change, haematoma, vomiting, skin burn, brachial plexus injury and nodule rupture, as well as abscess formation and hypothyroidism.

Dr. Jean Palussière (Bordeaux/FR) presented ablation for **small breast malignancies**, an option thanks to ever earlier detection. The literature deals mostly with breast cancer in the elderly. RFA results so far indicate good long-term efficacy. However, there is a risk of failing to detect the occult microscopic extent of the tumour; continuous follow-up, preferably with MRI, is essential. The ablation zone often remains palpable, requiring clear communication with the patient; there is a risk of scarring skin burns; and, in the long term, nipple retraction may occur. Cryo is less painful, can be performed under local anaesthesia, and can treat lesions both larger and closer to the skin.

Prof. Constantinos Sofocleous (New York, NY/US) discussed **adrenal tumour ablation**, an option when surgery is not possible, or in case of recurrence after resection. It requires general anaesthesia and continuous arterial blood-pressure monitoring. Reported technical success rates have been very high. For solitary adrenal tumours, results have been particularly good, with one study indicating that half of the patients were cured at a mean follow-up of 29.8 months. Complications are rare, but practitioners must be ready to intervene should a hypertensive crisis due to catecholamine secretion or bleeding occur. Ablation could soon serve as first-line therapy for select smaller adrenal tumours.

Dr. Alice Gillams (London/UK) addressed **lymph node ablation**, which can be effective, but requires careful patient selection and excellent staging. It is indicated for isolated, loco-regional recurrence, and mostly used when surgical and radiotherapy options have been exhausted. Practitioners must think carefully about potential collateral damage, keeping a 1 cm distance from the edge of the ablation to critical structures. Low-power and short treatment times often suffice. The initial end-point is devascularisation on US, CEUS or CT, with shrinkage or disappearance visible at follow-up.




With **prostate cancer** caught earlier and a lower proportion of patients presenting with metastases, focal ablation is of increasing interest, noted Dr. David Woodrum (Rochester, MN/USA). Benefits include an attractive side-effect profile; that future surgery and radiotherapy remain possible; and that it may offer a low-risk treatment for patients in the "watchful waiting" category. However, practitioners must make sure they are not inadequately treating patients. Overall, long-term data is lacking. Currently, cancer in the native prostate gland is being treated with MRgFUS, cryo- and laser ablation. US-guidance has also been used, but MRI is superior. For recurring prostate cancer, MR-guided cryo- and laser ablation offer additional treatment options to those who qualify neither for surgery nor further radiation.

Molecular oncology and translation into the clinic

In a joint session with the WCIO, Prof. Goldberg discussed **oncogenic pathways and their relevance to interventional oncology**. Practitioners must better understand systemic effects triggered by procedures they perform. For example, ablation may influence organ homeostasis, residual tumour growth and tumour initiation. Tackling this requires determining which cytokines induce cellular reactions that occur post-RFA. Research indicates that various cytokines are elevated following ablation, with cytokine IL-6 substantially elevated a week after the procedure. Anti-cytokine drugs may reduce unwanted systemic effects, with research on RFA with adjuvant liposomal anti-IL6 siRNA, for example, showing a significantly reduced tumour growth rate. The issue is not limited to ablation; recent data suggests that TACE can induce pro-oncogenic changes. Successfully manipulating these unintended side-effects requires closer cooperation with molecular oncologists.

Dr. Wood outlined developments relating to **tumour hypoxia**. Current research efforts are scrutinising the interaction and dynamics of hypoxia, angiogenesis, inflammation and immunomodulation, as well as of Hsp70, toll-like receptors, HIF1a, VEGF, IL-6, stem cells and gene expression. With some tyrosine-kinase inhibitors more effective on hypoxic tumours, integrating rational drug choices is a priority. In addition, imageable drugs hold considerable promise. Other future developments include identifying optimal combinations of various focal, regional and systemic treatments.

Prof. Jens Ricke (Magdeburg/DE) addressed **immunomodulation and radioembolisation**. The goal is to overcome the immune shielding of tumours. Anti-CTLA-4 and anti-PD-1 (Ipilimumab and Nivolumab) are getting much attention, and have been approved for melanoma to squamous non-small-cell lung cancer. Radiation induces immunologic cell death, thus enhancing or enabling immunologic response. Radiotherapy promotes endogenous vaccination, and immune checkpoint modulators (like CTLA-4 and PD-1 block) outperform immunogenic tumour shielding. When combining immunology and radioembolisation, the less of a tumour load involved, the better the synergy.

Prof. Jeff Geschwind (Baltimore, MD/US) stated that tumour glycolysis is a key hallmark of cancer, and the final common pathway to most, if not all, tumours, making it an interesting target. A number of drugs specifically targeting **tumour metabolism** are under development. These include 3-Bromopyruvate, which contains the key ingredient of Bromine. Animal studies on intra-arterial delivery of 3-Bromopyruvate in free form showed results as early as two hours following treatment. Subsequent efforts have focused on delivering it systematically, with researchers recently succeeding in doing so by way of nano-molecular microencapsulation, a breakthrough development.

Dr. Rafael Duran (Lausanne/CH) tackled **image-guided drug activation**. Various hypoxia-targeting therapies have been developed, including hypoxia-activated prodrugs (HAPs), with TH-302 currently the most advanced in clinical development. Its efficacy in systematic delivery has been demonstrated. There might be a synergistic effect when combining conventional chemotherapy with TH-302; this is being explored in various trials, including two Phase III randomised controlled trials. Moreover, HAPs can be used in the interventional oncology setting, with the combination of TH-302 and cTACE recently showing particular promise. However, additional studies are needed.

The speakers and moderators from the Joint Session with the WCIO

Prof. Alban Denys (Lausanne/CH) presented efforts to develop a **DNA repair inhibitor**. Currently available molecules targeting DNA repair pathways all target only one of the two main enzymes involved in the repair. D BAIT, developed by DNA Therapeutics, is a double DNA fragment which, injected systemically or locally, enters cells and acts as an activator of the different molecules. As a result, all enzymes are trapped and can no longer actively repair DNA. Having shown promise in combination with TACE, it could also be combined with ablation systems: research on mice has indicated that D BAIT enhances the effect of RFA. Ongoing research efforts are focusing on different cell lines and variations in injection protocols.

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