Radiological Interventions in HCC

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HCC: Interventional Radiology

♦ Role of Interventional Radiology in the management of HCC
  - An overview of current techniques
  - Innovative techniques
HCC: Interventional Radiology

Culinary Analogy

**LE PRINTEMPS**
**MENU DEGUSTATION** $480
Imaginé par Joël Robuchon

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**Le Caviar**
une infusion de sorbet arabe, en surprise
Caviar on aaed in a sorbet arabic as a surprise

**L'Oursin**
sur un délice fondant de caviar éclaté en gelée
Sea urchin on a delicious cracked caviar in gelée

**Les Asperges**
un blanc-bleu d'asperges, brioche blanche et dans une violette de pain doré
Asparagus Hello Kitty with blue cheese, brioche white bread and a golden crust

**La Saint-Jacques**
l'as de paille, l'ai de coco frit et un condiment de citron et de fumée
Saint-Jacques, coconut fried and a lemon and smoke condiment

**Les Crustacés**
un œuf, égoutté laitier et l'ail d'un musange tout recuit, le boursin graisse d'ail au curry et fines graines de charpentier
Crustaceans egg, let out dairy and garlic of a musquid all cooked, the boursin grease of curry and fine seeds of carpenter

**Les Fétas**
un vin vinifié secs à la saumure sous un voile d'oléagineux doux
Wine vinified dry in saumure under a veil of sweet olive oil

**Le Foie gras**
en papillote de choux vert aux jeunes baumiers
Foie gras in a papillote of green cabbage with young beeches

**Le Saumon**
avec une mayonnaise au gingembre et une filtrante légèrement fumée
Salmon with ginger mayonnaise and a lightly smoked filtrant

**Le Véau**
un côte au gratin avec un jus de viande et de légumes de la vallée
Veal chop au gratin with meat and vegetable juices from the valley

**Le Soja**
les javanes poudreuses salées comme un ruban aux endives de chicon noir et mimosette
Soybean powder with salted as a ribbon with black endives and mimosa

**L'Orange**
restée vert de l'orange croustillante à la vanille poivronnée
Light orange crunchy with vanilla peppered

**Le Chocolat**
Sphère croquante aux petits perles, éclate de fruit de la passion
Chocolate crispy sphere, passion fruit splash

**Le Moka - le Thé**
envoûte de mignardises
Table 1. Summary of interventional procedures used in hepatocellular carcinoma (HCC) management

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Aim</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein embolization</td>
<td>Induce atrophy of embolized area and hypertrophy of contralateral lobe</td>
<td>Glue or alcohol and coil</td>
</tr>
<tr>
<td>Thermoablation</td>
<td>Induce destruction of tissue through thermal techniques</td>
<td>Radiofrequency ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laser ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microwave ablation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cryotherapy</td>
</tr>
<tr>
<td>Chemoablation</td>
<td>Induce coagulative necrosis using chemotherapeutic cytotoxic effects</td>
<td>Percutaneous injection of ethanol or acetic acid</td>
</tr>
<tr>
<td>Transarterial chemoembolization</td>
<td>Significant necrosis of tumour</td>
<td>Ethiodized oil plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>any of various anticancer agents</td>
</tr>
<tr>
<td>Drug-eluting beads</td>
<td>Induce selective sustained release of chemotherapy over a long period of time</td>
<td>Polyvinyl alcohol hydrogel plus chemotherapy</td>
</tr>
<tr>
<td>Transarterial radioembolization</td>
<td>Cannulation of the hepatic artery with radiotherapy</td>
<td>$^{131}$I-Labelled ethiodized oil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{90}$Y-Loaded microspheres</td>
</tr>
</tbody>
</table>

HCC: Portal Vein Embolisation

- Performed prior to extended liver resection

- Aims
  - To induce progressive atrophy of the embolised territory
  - To induce hypertrophy of remaining non-tumour containing liver parenchyma (Future Liver Remnant – FLR)

- Used when FLR <20-30% of initial total normal liver volume (or <50% in fibrotic / cirrhotic livers; FLR gain less in cirrhotic patients)
HCC: Portal Vein Embolisation

◆ Technique

- Percutaneous transhepatic ipsilateral approach (via liver to be resected) - preferred approach
- Distal portal branch accessed under ultrasound guidance
- Vascular sheath inserted over a guide wire
- Flush portography performed to assess for variations in portovenous anatomy
- Portal venous pressures measured throughout the procedure; significant portal hypertension contraindication to hepatic resection
HCC: Portal Vein Embolisation

◆ Technique

- Embolic materials
  » Glue
  » Alcohol
  » Particles (PVA)
  » Coils

- Puncture tract embolised with coils
HCC: Portal Vein Embolisation

◆ Outcomes

- Degree of hypertrophy after PVE dependent on degree of underlying liver disease
- Normal liver regenerates at 2 weeks post-procedure at a rate of 12 to 21cm$^3$/day with sufficient hypertrophy typically within 2 - 4 weeks
- Cirrhotic livers regenerate at 9cm$^3$/day and sufficient regeneration can take ≥4 weeks
Local Ablative Techniques: Thermal

- Tumour destruction by heating or freezing
  - Radiofrequency Ablation (RFA)
  - Microwave Ablation (MWA)
  - Laser ablation (laser interstitial thermal therapy LITT)
  - Cryoablation
Local Ablative Techniques: Thermal

RFA

◆ Mechanism

- Electrical generator converts normal electrical AC current (50Hz) to AC current in radiofrequency range (500 kHz)

- RF current at exposed (non-insulated) electrode tip of shielded needle probe causes ‘to-and-fro’ agitation of surrounding electrolytes (local ionic agitation) → frictional heat
Local Ablative Techniques: Thermal

RFA

- Temp >50° C → coagulative necrosis occurs in surrounding tissue
- With continued propagation of heat, an approximate 3.0-3.5cm sphere of focal thermal injury with each ablation is achieved (experimental studies*)

*R-Cool-tip™ RF Ablation System E Series
Tissue Verification Testing Protocol
Ablation zone is dependent upon tissue vascularization, type, temperature and impedance. Ablation zone testing was performed in healthy ex vivo bovine 20°C liver.
Local Ablative Techniques: Thermal

RFA

- **GOAL** → Complete ablation of target tumour plus a 5-10mm circumferential cuff of adjacent NORMAL hepatic parenchyma (clear margins to prevent / minimize local recurrence)

- Basis of approximate 3cm sphere of thermal injury
  - Tumour size
    - <2-3 cm diameter : 1-2 ablations
    - 3-4 cm diameter : Multiple electrode insertions / overlapping ablations
    - >4 cm diameter : Risk of incomplete ablation

- Duration of single procedure depends on number of ablations performed (single ablation takes about 12 minutes duration)
Local Ablative Techniques: Thermal

RFA
Local Ablative Techniques: Thermal

RFA

‘Heat-sink’ effect

Thermal profile of RFA Tissue Heating
Local Ablative Techniques: Thermal

MWA

- What is Microwave?
  - Form of electromagnetic radiation (*E-M* radiation)

Electromagnetic Spectrum

- RF spectrum
  - Household appliances to shortwave radio to super-high frequency
  - Electrosurgery 200 kHz-3.3 MHz
  - Cool-tip is 470-480 kHz

- MW Spectrum
  - Approved microwave frequency bands are at 915 and 2450 MHz (regulated by FCC)
  - Cell phones, cordless phones
Local Ablative Techniques: Thermal

MWA

♦ Mechanism

- Microwave used for tumour ablation works on a similar principle as a microwave oven

- Microwave energy causes the water molecules to spin, creating friction, resulting in heat generation

- Microwave oven radiates electrical field inwards, microwave antenna radiates electrical field outwards
Local Ablative Techniques: Thermal

◆ **RFA**
  - Tissue – ionic agitation
    - Amount of current delivered is based on the impedance of tissue
    - Ions focused at electrode / current density

◆ **MWA**
  - Tissue – spinning water molecules
    - Action caused by movement of water molecules against each other
    - Mechanism of friction is different, but the source of heat is friction in both

**RF current at exposed (non-insulated) electrode tip of shielded needle probe causes ‘to-and-fro’ agitation of surrounding electrolytes (local ionic agitation) → frictional heat**

**Spinning water molecules**
Local Ablative Techniques: Thermal

MWA

- **Evident™ MWA System Antenna Design**
  - 915 MHz
  - 45 W power maximum
  - Time settings
    - One minute increments
    - Maximum 10 minutes
Local Ablative Techniques: Thermal

- **MWA**

  - Tumour location – presence of abutting vessels
    - Less perivascular tissue cooling effect (↓ ‘heat sink’)
    - More effective perivascular tumour kill
    - Decreased recurrence rate?
Local Ablative Techniques: Thermal

MWA

Microwave Thermal Ablation ‘Heat sink’ effect grading (based on coagulation margin contour at hepatic veins) in animal study (Ref: Yu NC et al. JVIR 2008; 19:1087-1092)

- **0 - None / minimal**
- **1 - Mild**
- **2 - Moderate**
- **3 - Severe**

Blunting of margin contour

61% / 24% / 15% / 0%
Local Ablative Techniques: Thermal

MWA

- Tumour location - presence of abutting vessels
  - Less perivascular tissue cooling effect (‘heat sink’)
  - More effective perivascular tumour kill
  - Decreased recurrence rate?

- More risk of vascular damage
  - May lead to large areas of infarct
  - Careful selection of cases
  - Rule of thumb → Do not plan ablation zones that include large circumference of critical vessel

Post-MWA Hepatic vein thrombus
Local Ablative Techniques: Thermal

Cryoablation

◆ Oldest thermoablative technique for liver malignancy *(Ref: Cooper IS. N Engl J Med 1963; 268:743-9)*

◆ Circulation of coolant (liquid N2/argon) through metallic cryoprobes inserted into the tumour

◆ Mechanism
  
  - Rapid freezing of tumour tissue to subzero temperatures (-20°C to -60°C)
    
    » Intracellular ice formation → direct cellular structure damage, protein denaturation and cell membrane rupture
  
    » Extracellular ice formation → indirect cell death from microvascular occlusion and osmotic dehydration
Local Ablative Techniques: Thermal

Cryoablation

- Cryoprobe inserted into tumour under imaging guidance (US / CT)
- Liquid N2 circulated through probe until entire tumour + 1cm margin frozen
- Freezing process monitored easily and accurately by real-time US
  - Formation of enlarging *ICE BALL*
  - Hypoechoic region with surrounding hyperechoic rim and acoustic shadowing
  - Extreme cold maintained for at least 10-15 minutes to ensure lethal-ice temperatures have been reached
- Optimal tumour characteristics
  - Size - <5cm
  - Location - away from major vascular / biliary structures
Local Ablative Techniques: Thermal

Laser Interstitial Thermal Therapy (LITT)

- Laser thermal ablation, Interstitial laser therapy, Interstitial laser photocoagulation

  - Laser fibre (0.5-2.5mm diameter) coupled to energy source (Neodymium:yttrium aluminium garnet [Nd:YAG] diode laser) inserted into liver tumour
  - Nd:YAG laser emits low energy (3-20W) laser light at wavelength of 1064nm for 2-20 minutes
  - Photons from laser light interact directly with naturally-occurring tissue molecular chromophores -> heat production
  - Slow heating
    » Induces thermal coagulation of tumour tissue >60°C
    » Prevents carbonisation and vaporisation of tissues (-> tissue coagulum)
    » Allows maximum optical tissue penetration (12-15 mm) + expansion of heat zone sufficient to destroy tumour
Local Ablative Techniques: Thermal

LITT

- Thermal lesions typically 10-15mm in diameter
- Marginally larger lesions with new laser fibre designs (sapphire-tipped laser fibres, cooled-tip applicators, cylindrical quartz diffusers)
- Larger lesions with multiple fibre system with beam splitters (4 fibres)
- MRI for imaging guidance and real-time thermal mapping during ablation
Chemoablation

◆ Chemical

- HCC – favourable physical characteristics
  » Soft texture
  » Fibrous capsule
  » Hypervascularity
  » Within firm cirrhotic liver

- Hot saline, chemotherapeutic drugs

- Percutaneous ethanol injection (PEI)

- Percutaneous acetic acid injection (PAI)
Chemoablation: PEI


- Mechanism
  - Cellular dehydration
  - Protein denaturation
  - Thrombosis of small vessels
  - Coagulation necrosis

- Sterile 95% / absolute alcohol

- Percutaneous injection via PEIT needle (Hakko, Tokyo, Japan; 20cm long 21G needle with closed conical tip and 3 terminal/side holes)

- Injection number and volume - tumour size, patient tolerance; multiple treatment sessions
Chemoablation: PEI
Chemoablation: PEI

◆ Limitations

- Inability to treat large size tumour
  » Complete necrosis in nearly all tumours <2cm vs up to 70% <3cm
  
- High local recurrence rate
  » Up to 33% in tumours <3cm
  » >43% in tumours >3cm
  
  » Geometric parameters variable and difficult to predict
    ◆ Poor extracapsular penetration
    ◆ Intratumoral septation
    ◆ Tumour vascularity
Chemoablation: PAI


- Acetic acid
  - Low pH, dissolves lipids, breakdown collagen cross-links
  - Advantages over ethanol
    » Stronger necrotising agent
    » Penetrating tumour capsule and intratumoral septa
    » 1/3 volume of ethanol
  - Few centres worldwide
Regional Transarterial Therapy

◆ Techniques

- Transarterial chemotherapy (TAC)
- Transarterial bland embolisation (TAE)
- TRANSARTERIAL CHEMOEMBOLISATION (TACE)
- TRANSARTERIAL RADIOEMBOLISATION (TARE)
Regional Transarterial Therapy

**Principle**

- Normal liver blood supply
  70-80% PV, 20-30% HA
- Malignant hepatic lesions
  almost exclusively supplied by the arterial system
- Microvascular density of hepatic tumours ~3-200x higher than surrounding normal liver parenchyma
Regional Transarterial Therapy

◆ Rationale

- Utilizes ‘PARASITIC’ effect of tumour on arterial system
- Selective delivery of cytotoxic/ischaemia-inducing agents into HA branches resulting in
  » Highly localised entrapment of agents within tumour (high tumour dose) → tumour necrosis
  » Tumour ischaemia increasing drug dwell time within tumour and low systemic toxicity
  » Sparing of normal liver parenchyma with minimal toxicity effects to the rest of normal liver and to the patient’s body
Transarterial Chemoembolisation

◆ TACE (Conventional)
  - Chemotherapeutic agents – *Mitomycin-C, Adriamycin, Cisplatin*
  - *Lipiodol* (iodinised poppy seed oil) – retained in tumour (high tumour drug concentration)
  - Polyvinyl alcohol (PVA) particles / *Gelfoam* sponge
    - tumour ischaemia inhibiting drug washout (prolongs drug contact time with tumour) and low systemic toxicity
  - Procedure repeated at 8-12 weeks or depending on patient tolerance and tumour response
Transarterial Chemoembolisation

◆ TACE (Precision)

- DC Bead™ Drug-Eluting Beads (Biocompatibles UK Ltd. [BTG International Group])
  » Novel drug delivery embolization system with N-Fil Technology™
  » Produced from biocompatible polyvinyl alcohol (PVA) hydrogel polymer that has been modified with sulphonate groups
  » Low-compressible microspheres capable of being loaded with, and releasing, high doses of chemotherapeutic agents in a controlled and sustained manner
  » Blue-tinted to aid visualisation
  » Available in colour-coded vials with a range of sizes- 100-300μm, 300-500μm, 500-700μm and 700-900μm
Transarterial Chemoembolisation

**DC BEAD™ CONCEPT**

- **DC Bead™** Drug-Eluting Beads introduced via a catheter into vessel feeding the tumour
- Beads embolize tumour
- Drug delivered locally – eluting into the tumoral tissue over several weeks; *local, controlled* and *sustained* dose of doxorubicin to the tumour(s)
- Tumour vessel occluded and tumour tissue killed
- Drug-Eluting Bead portfolio allows the combination of drug dose, bead size and volume to be tailored to each patient’s needs
Transarterial Chemoembolisation

Schematic showing the relative drug distribution for standard arterial chemotherapy vs. conventional TACE vs. precision TACE

Transarterial Radioembolisation

- External radiation of liver cancer is not effective
  - Radiation tolerance of liver is 30 Gy
  - Tumouricidal radiation dose is > 70-90 Gy
  - Choice of inadequate radiation dose to tumour vs radiation hepatitis

- Concept of *Targeted Therapy* using radioactive isotopes

- Also called *Selective Internal Radiation Therapy (SIRT)*

- SIRT gives adequate radiation to the tumour with little radiation to the rest of the liver and to the patient’s body
Transarterial Radioembolisation

External beam radiation causing Radiation-Induced Liver Disease

SIRT 100-1,000+Gy to tumour

Gy: 20 30 40 50 60 70 80 90 100

Tumoricidal dose Adenocarcinoma

Transarterial Radioembolisation

◆ Selective Internal Radiation Therapy (SIRT)

- Radioisotopes
  » Achieve targeted delivery into selective arterial supply of liver tumour/s
  » Compounded onto a delivery vehicle – microspheres – that selectively deposits into tumour tissue / vasculature
  » Yttrium-90
Transarterial Radioembolisation

◆ Transarterial $^{90}$Yttrium radioembolisation

- $^{90}$Y characteristics
  » Pure β-emitting isotope with high average energy (0.936 MeV)
  » Limited tissue penetration (mean 2.5mm, maximum 11mm)
  » Short half-life (64 hours)
  » Radiation dose of 100-1,000+ Gy to tumour

- Mechanism
  » $^{90}$Y incorporated into millions of glass microspheres (TheraSphere®, BTG International Canada Inc, Ottawa, ON, Canada) / biocompatible resin-based microspheres (SIR-Spheres®, SIRTeX Medical Inc, Sydney, NSW, Australia)
  » Selectively injected into hepatic artery / branch
  » Radioactive microspheres embedded in pre-capillary end-arterioles of tumour, delivering intense local (tumour) radiation → RADIOEMBOLISATION
Transarterial Radioembolisation

- Preliminary hepatic angiography + $^{99m}$Tc-MAA lung shunting scan
  - Hepatic arterial anatomy
  - Extrahepatic and hepatopulmonary shunting -> risk of fatal radiation pneumonitis
  - Shunt fraction >10% - dose reduction; >20% - precludes use of $^{90}$Y internal radiation therapy
Transarterial Radioembolisation

60-year old Chinese female

CT scan 14 Feb 2008
HCC nodules x 2

Hepatic angiogram
19 Feb 2008
Transarterial Radioembolisation

8 April 2008  (7 weeks post-treatment)
20 May 2008  (13 weeks post-treatment)
1 July 2008  (19 weeks post-treatment)
Innovative Techniques

- High intensity focused ultrasound (HIFU)
- BrachySil® therapy
- Photodynamic therapy
- Irreversible Electroporation (IRE)
Innovative Techniques

What is HIFU?

- Conventional Ultrasound in diagnostic imaging
  - Low intensity ultrasound energy propagates harmlessly through tissues

- High Intensity Focused Ultrasound (HIFU)
  - Extracorporeal US source - US beam carrying sufficient energy concentrated by tight focus onto target
  - Energy within focal volume causes local rise in temperature → thermal tissue necrosis
  - *No probe or needle placement* required for ablation as opposed to most other tissue ablation techniques
Innovative Techniques

HIFU

- Frequencies ranging from 0.8-3.2 MHz

- Range of acoustic intensity within focal field (Focal Intensity) 5,000 – 25,000 W/cm²

- Peak compression pressures up to 70 MPa; peak rarefaction pressures up to 20 MPa
Innovative Techniques

HIFU

- Spatial peak-temporal average intensity $I_{SPTA}$ - good indicator of thermal ultrasound effects
- The spatial peak-pulse average intensity $I_{SPPA}$ - an indicator of potential mechanical bioeffects and cavitation

**TABLE 14-9  TYPICAL INTENSITY MEASURES FOR ULTRASOUND DATA COLLECTION MODES**

<table>
<thead>
<tr>
<th>MODE</th>
<th>PRESSURE AMPLITUDE (MPa)</th>
<th>$I_{SPTA}$ (mW/cm²)</th>
<th>$I_{SPPA}$ (W/cm²)</th>
<th>POWER (mW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-scan</td>
<td>1.68</td>
<td>19</td>
<td>174</td>
<td>18</td>
</tr>
<tr>
<td>M-mode</td>
<td>1.68</td>
<td>73</td>
<td>174</td>
<td>4</td>
</tr>
<tr>
<td>Pulsed Doppler</td>
<td>2.48</td>
<td>1,140</td>
<td>288</td>
<td>31</td>
</tr>
<tr>
<td>Color flow</td>
<td>2.59</td>
<td>234</td>
<td>325</td>
<td>81</td>
</tr>
</tbody>
</table>

Adapted from compilation of data presented by the American Institute of Ultrasound in Medicine. Note the difference in units for $I_{SPTA}$ (mW/cm²) versus $I_{SPPA}$ (W/cm²).
Innovative Techniques

HIFU

- Each ablation sonication (10-25 seconds) destroys small volume of tissue
Innovative Techniques

HIFU

Current technical limitations with transcutaneous ablation of liver tumours

- Small focused zone of tissue necrosis (< 1cm)
  - Multiple repeated treatments along same plane and in 3-D
  - Accuracy of repeated targeting limited; requires computerised image guidance systems
- Precision of targeting limited by patient’s breath holding
- Thermal ablation process cannot be accurately monitored by US (acoustic shadowing by released gas bubbles) → MRI thermal mapping
- US energy absorbed by overlying bone / air → difficult to treat lesions underneath rib cage or in subdiaphragmatic location
Innovative Techniques

BrachySil® Therapy

- Brachytherapy in unresectable hepatocellular carcinoma
- BIOSP-201: A Proof of Concept Study of 32P Biosilicon™ in Patients with Unresectable Hepatocellular Carcinoma (HCC)
- Collaboration with pSiOncology (Singapore)/pSiMedica (UK)
- 32P
  - Physical half-life of 14.3 days
  - Maximum tissue range approximately 8mm
  - New microparticle system using porous silicon (Biosilicon™) as carrier matrix for 32P -> BrachySil®
Innovative Techniques

BrachySil® Therapy

◆ Protocol 32P SGH Study VI:
  
  *A Performance Assessment Of The Use Of The SIMPL™ Needle For Brachytherapy Implantation Of Non-Radioactive Material In The Pig Liver*

◆ A safety assessment of lung shunting following 32P BioSilicon™ implantation in pig liver.

*Chow PKH, Goh ASW, Lo RHG et al. 2006 pSiOncology Pte. Ltd., Singapore*
Innovative Techniques

BrachySil® Therapy

- First-in-human clinical safety study using single dose of $^{32}$P Brachysil® given intra-tumorally to patients with unresectable HCC
  - Patients enrolled in SGH between May 2004 and March 2005
  - Assessed by multidisciplinary clinical team and counselled with regards to therapeutic options
  - Evidence of disease defined by
    » At least 1 measurable lesion >2cm (CT scan)
    » ≤5 lesions in the liver
    » No single lesion >15cc volume (3cm diameter)
  - ECOG performance status 0-2
  - Okuda Stage I and II
  - Life expectancy > 12 weeks
  - Adequate haematologic / renal / hepatic functions
  - Exclusion criteria
    » Encephalopathy
    » Prior radiotherapy
    » Significant history of cardiac disease
    » Serious active infection
  - Maximum 3 tumours per patient treated
  - Intratumoral implantation of $^{32}$P Brachysil under radiological imaging guidance and local anaesthesia /conscious sedation
Innovative Techniques

BrachySil® Therapy

SIMPL™ Implantation Needle

Syringe Infusion Pump
Innovative Techniques

BrachySil® Therapy

Post-RFA recurrence:
Pre-implantation

Implantation
Innovative Techniques

BrachySil® Therapy

Post-implantation follow-up CT scan

at 3 months

at 6 months
Innovative Techniques

BrachySil® Therapy


ASW Goh, AYF Chung, RHG Lo, TN Lau, SWK Yu, M Chng, S Satchithanantham, SLE Loong, DCE Ng, BC Lim, S Connor and PKH Chow. *Int J Radiation Oncology Biol Phys* 2007; 67(3):786-92

- Successful Brachysil® implantation in 8 patients (13-74 MBcq)
- All targeted tumours were responding at 12 weeks
- Complete response (100% regression) in 3 lesions
- At the end of study
  » 2 complete responses
  » 2 partial responses
  » 3 stable diseases
  » 1 progressive disease

- *Conclusion*: Percutaneous implantation of this novel $^{32}$P brachytherapy device into hepatocellular carcinoma is safe and well tolerated. A significant degree of antitumour efficacy was demonstrated at this low dose that warrants further investigation.
Innovative Techniques

Photodynamic Therapy

- **Mechanism**
  - Interaction between photosensitizer administered systemically and light of particular wavelength → tissue necrosis? Release of O2 free radicals

- **Phase III clinical trial with Light Sciences Oncology (Snoqualmie, WA, USA)** in the treatment of patients with unresectable hepatomas
  - Objective: To assess the survival and safety of patients treated with *Litx™* versus a control group receiving the standard of care at each investigative site.
  - Target: Approximately 200 patients at sites in Singapore (NCC, SGH), Hong Kong, China, South Korea, the Philippines, Malaysia and Thailand
  - Completed recruitment in Sept 2012; awaiting results analysis

*Litx™ Technology*
Innovative Techniques

Photodynamic Therapy

◆ **Litx™ (Light Infusion Therapy™)**

- Device - Proprietary flexible light emitting diode (LED) array connected to power supply by catheter-like sheath containing electrical leads
- Drug - LS11 (talaporfin sodium) light-activated, water-soluble (inert molecule with no biological activity)
- Insertion of LED array into the tumor through the skin in a biopsy-like procedure under imaging guidance
- IV injection of LS11 (dose calculated based on body weight)
- LED array activated 10-15 minutes post-injection
- Light from the array energizes LS11 molecule -> reacts with nearby O2 molecules, converting molecular oxygen to singlet oxygen/free radicals -> kills tissue within a zone surrounding the LED array + shuts down tumour blood supply within that zone
- Light source typically on for approximately 2.5-3.0 hours to maximize the effect on the tumor and to assure continued blood vessel closure
- Simple system containing all treatment-required components included in a single-use package
Innovative Techniques

**Litx™ (Light Infusion Therapy)**

**LED—Light Emitting Diode**

**Talaporfin Sodium LS11**

**Catheter-like sheath (electrical leads)**

**Battery & Timer**

**Tumour**
Innovative Techniques

Green filters fitted on ceiling lights in Procedure Room and OT

*Litx™ (Light Infusion Therapy)*
Innovative Techniques

Photodynamic Therapy

Post-RFA 2 months - recurrence

LiTx with multiple insertions

Post LiTx
Innovative Techniques

Irreversible Electroporation (IRE)

◆ New technology recently applied in HCC treatment
◆ Mechanism
  - Delivers pulses of electrical current up to 3kV to tumour cells
  - Produces electrical field creating microscopic pores (nanopores - **HOLES**) in cell membranes which are open permanently
  - Irreversible damage to homeostasis of cells → cell death by apoptosis
◆ Advantages
  » No effect on extracellular matrix; no heat or cold generated, thereby maintaining structural integrity of adjacent blood vessels and bile ducts
  » Does not cause fibrosis / scarring; treatment zone can be evaluated earlier
◆ Disadvantages
  » Patient under GA
  » Deep neuromuscular block
Innovative Techniques

IRE

- High-tech system that generates IRE - **NanoKnife**
- Approved by the Food and Drug Administration (FDA) for the ablation of soft tissue
- Currently used for lung, liver, prostate and kidney tumours
Innovative Techniques

IRE

- Allows extreme precision of killing tumour cells without causing collateral damage to adjacent tissue
  - Targeted soft-tissue cells killed
  - Blood vessels and other important structures in the area remain functional
HCC: Interventional Radiology

Summary

◆ Chemoablation, Local Ablation and Regional Transarterial Therapy
  - Evolved in the treatment of unresectable liver tumours
  - Treatment strategy guided by
    » Tumour characteristics
      ◆ Histology
      ◆ Size and number
      ◆ Anatomic location
    » Multidisciplinary Team approach
    » Institutional availability of equipment and expertise
  - TACE, RFA, (TARE) most widely used techniques
  - Newer innovative techniques emerging - ? viable treatment options in the future
Thank You
Local Ablative Techniques: Thermal

MWA

- 0 - None: 61%
- 1 - Mild: 24%
- 2 - Moderate: 15%
- 3 - Severe: 0%
Local Ablative Techniques: Thermal

MWA

- Tumour location – presence of abutting vessels
    » To determine influence of hepatic vein size on perfusion-mediated attenuation in adjacent microwave thermal ablation (approval of institutional animal research committee obtained)
    » 7 Yorkshire pigs
      - Under GA
        - Percutaneous (*n* = 2) or open (*n* = 5) MWA of liver
    » MW ablation
      - Multiple (5-12 / animal) US-guided, non-overlapping thermal lesions created within 1 cm of hepatic veins
      - Straight tip antenna, 5-10-minute ablation at 45 W
    » Histopathologic analysis of liver sections for degree of perivascular coagulation attenuation and correlation with vein size (small ≤3 mm; medium 3-6 mm; and large >6 mm)
Local Ablative Techniques: Thermal

MWA

◆ Tumour location – presence of abutting vessels
  » Results
    ◆ 63 of 103 sections (61%) - thermal injury extended to the vein wall around the entire circumference of the coagulation front without distortion of the ablation margin
      - 29 of 37 (78%) small, 27 of 48 (56%) medium, and seven of 18 (39%) large veins
    ◆ In 40 of 103 sections (38.9%) - varying degrees of concave distortion of perivenous ablation margins with significant correlation between vein size and heat-sink extent (*P* < .01)
    ◆ Thermal injury extended to the vascular wall in all sections without complete circumferential sparing of liver tissue
    ◆ Around 2 thrombosed veins, thermal lesions encased the vessels producing paradoxical convex ablation margins

» Conclusion: Although the ‘heat-sink’ effect was significantly dependent on hepatic vein size, the majority of pathologic sections exhibited no or minimal effect
Innovative Techniques

HIFU

◆ Experimental in West

◆ Most publications from China

  » 100 patients (62 primary and 38 metastatic liver cancers)
  » Improved clinical symptoms 86.6%; LFTs back to normal 83.3%; AFP reduced by >50% in 65.3%

  » Randomised trial comparing TACE vs TACE + HIFU in advanced HCCs
  » Median survival time 4.0 months vs 11.3 months (*P*=.004)
  » 6-month survival rate 13.2% vs 80.4% (*P*=.002)
  » 1-year survival rate 0% vs 42.9%
  » Median reductions in tumour size (% of initial tumour volume) at 1/3/6/12 months
    4.8%/7.7%/10%/0% vs 28.6%/35.0%/50.0%/50.0%
**Chemoablation: PAI**


- **Acetic acid**
  - Low pH, dissolves lipids, breakdown collagen cross-links
  - Advantages over ethanol
    » Stronger necrotising agent
    » Penetrating tumour capsule and intratumoral septa
    » 1/3 volume of ethanol
  - Few centres worldwide

- **2 RCTs comparing PAI vs PEI**
  - **Ohnishi** (Ohnishi K et al. *Hepatology* 1998; 27:67-72)
    » 2-year survival rate / 2-year recurrence rate : 92% / 8% vs 63% / 37%
    » No significant difference in complication rate
  - **Huo** (Huo TI et al. *Scand J Gastroenterol* 2003; 38:770-8)
    » No significant difference in survival rate
Transarterial Radioembolisation

Pre treatment          At 5 months          At 3 months            At 9 months
At surgery
Local Ablative Techniques: Thermal

MWA

- Clinical relevance
  - Large, fast ablations
    » Especially with multiple applicators
    » 5-6 cm ablations in 5-10 minutes
    » More care and monitoring needed!

Triple clustered applicators
  45 W
  10 min → 6 x 5 cm
Transarterial Chemoembolisation

◆ TACE (Precision)
  - Microspheres loaded with
    » Doxorubicin - Drug-Eluting Bead: DEBDOX™
    » Irinotecan - Drug-Eluting Bead: DEBIRI™

Before loading
(Light Microscopy)  After loading Before delivery
After delivery - No clumping/fragmentation
Local Ablative Techniques: Thermal

RFA

Pathological Tissue Reaction to Thermal Injury
Transarterial Chemoembolisation

HCC - TACE

Post-TACE 2 months
Innovative Techniques

HIFU

- Tumour lesion may be located deep within the liver
- Overlying skin and liver tissue unharmed
- Sharp boundary between ablated (dead) tissue and viable tissue
Innovative Techniques

HIFU

- Creating fire with magnifying glass using sunlight
Innovative Techniques

HIFU

- Overlapping sonications performed until all tumour tissue ablated
- Number of sonications and treatment strategy based on imaging data acquired prior to ablation procedure (US or MRI depending on apparatus type)