LIVER CANCER AND LIVER METASTASES
NEW TECHNIQUES FOR ELDERLY

Nicola de’Liguori Carino
Consultant HPB Surgeon
HPB Unit
North Manchester General Hospital
Salford Royal University Hospital
Manchester, UK

11th Annual SIOG Meeting, Paris November 4-5
PREOPERATIVE ASSESSMENT
CPEX is a non-invasive integrated assessment of cardiovascular and pulmonary function both at rest and under stress. It replaces a traditional exercise stress test. It combines measurements of ventilation, respiratory gas exchange, ECG, BP and physical response before, during and following an exercise.

- Distinguish whether shortness of breath is caused by heart failure or lung disease
- Identify the anaerobic threshold
- Answer questions relating to exercise intolerance, exercise limitation and patient management
Cardiovascular measurements
1. Resting and exercise 12 lead ECG
2. Resting and exercise blood pressure
3. Oxygen consumption (V02)
4. Anaerobic threshold (AT)
5. Stroke index (indication of left ventricular function)

Respiratory measurements
1. Resting lung spirometry testing
2. Exercise flow volume loop recordings
3. Resting and exercise pulse oximetry monitoring
4. Respiratory rate (RR)
5. Tidal volume (Vt)
6. Minute ventilation (VE)
7. Carbon dioxide (VC02) production
8. Ventilatory equivalents (VEV02 and VEVC02)
9. End tidal oxygen and carbon dioxide tensions
10. Breathing reserve (BR)
11. Breathing efficiency
Systemic postoperative response is mainly related to cardiovascular and respiratory capacity and to the ability to maintain increased performance, identify the AT threshold appears to be one of the best predictors of outcome in major surgery.

Older P et al. Chest 1999

A cut off value of AT 11ml⁻¹ kg⁻¹ predictor of high risk of post operative mortality in elderly patients undergoing major abdominal surgery.

Smith AT et al. Anaesthesia 2009
✓ Indications, surgical techniques and follow-up are the same in use for younger patients.

✓ Elderly patients benefit from repeat hepatectomy as younger patients with no significant increase in peri-operative mortality and morbidity<sup>1</sup>

✓ No established protocols or guidelines for dedicated peri-operative care

<sup>1</sup>R. Adam et al. British Journal of Surgery 2010
Several studies proved that liver resection for CRLM in the elderly is now established as safe and effective as in young patients\textsuperscript{1-3}

<table>
<thead>
<tr>
<th>• Peri-operative mortality 3.8%</th>
<th>morbidity 32.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• OS</td>
<td>3-years 57%</td>
</tr>
<tr>
<td></td>
<td>5-years 36%</td>
</tr>
<tr>
<td>• DFS</td>
<td>3-years 37%</td>
</tr>
<tr>
<td></td>
<td>5-years 25%</td>
</tr>
</tbody>
</table>

\textsuperscript{1} U. Kulick et al. World J. Surgery 2011
\textsuperscript{2} R. Adam et al. British Journal of Surgery 2010
\textsuperscript{3} N. de’Liguori Carino et al. Crit Rev Oncol Hematol. 2008
Radiofrequency ablation is a thermoablative technique that produces tumour destruction by heating cancer cells to temperatures exceeding 60°C.

- The electrodes are inserted into the target tumour area (or areas) using imaging guidance (CT or US) during surgery (open or laparoscopic), or percutaneously under local anaesthesia.
Radiofrequency (RF) ablation may be indicated as the primary treatment for liver metastases where the patient is unfit for surgery or in the treatment of unresectable post-resection recurrence.

It may also be used as an adjunct to hepatic resection to ablate small-volume disease in the future remnant liver.

In elderly pts with resectable disease but less favourable tumour characteristics, RFA may provide better quality-adjusted life expectancy then other strategies (BSC, SC, LR)\(^1\)

\(^1\) S. Yang et al ASCO 2010
RFA: EFFICACY & SAFETY

• Several non randomized studies showed significant better OS and DFS for patients treated with LR vs RFA\(^1-4\)

• Safe procedure with severe complication varying from 1 to 3\(\%\)^\(^1,4-5\)

1 Sutherland LM et al, MSAC report, 2003
2 Abdalla EK et al, Ann. of Surgery, 2004
3 Gleisner AL et al, Arch. of Surgery, 2008
5 Veltri A et al, Cardiovascular & Interventional Radiology, 2008
Macrowave ablation, by inducing an ultra-high-speed (2450 MHz) alternating electric field, is a technique that aims to destroy tumours by heating cells, resulting in localised areas of necrosis and tissue destruction.

The electrodes are inserted into the target tumour area (or areas) using imaging guidance (CT or US) during surgery (open or laparoscopic), or percutaneously under local anaesthesia.
MWA: INDICATIONS, EFFICACY AND SAFETY

- Same indications as for RFA
- No contraindication for elderly pts
- Faster heat generation over a larger volume of parenchima
- Able to ablate larger tumors (> 2 cm)
- Produce more round necrotic areas
- More efficacy to burn tumors in proximity of large blood vessels
- No strong evidence of its superiority vs RFA in achieving OS or DFS in small tumors
- Few discordant evidence of its effect when compare to LR
- Safe procedure with very few complication

1 Shibata T et al, Cancer, 2000
2 Tanaka K et al, Surgery, 2006
3 Hompes R et al, EJSO, 2010
SIRT: SELECTIVE INTERNAL RADIATION THERAPY
(Radio-embolization or mini-brachytherapy)

- Glass or resin microspheres containing yttrium-90, designed to embolise into small vessels around the metastases

- Microspheres are selectively injected into branches of the hepatic artery via a percutaneous approach

- Delivering high doses of localized ionising radiation.
SIRT: INDICATIONS

- Non resectable, non ablateable CRLM
- No contraindication in elderly
- Chemotherapy naïve pts non suitable for systemic chemotherapy and with no extrahepatic disease
- Pts resistsants to multiple lines of systemic chemotherapy and with no extrahepatic disease

NICE guidelines 2011
**SIRT: EFFICACY**

- Few non uniform RCT

- Chemo naïve/chemo refractory pts SIRT+HA chemotherapy vs HA chemotherapy alone:
  - No benefit in mean survival\(^1\)
  - Significant longer median time to progression

- Chemo naïve pts SIRT+systemic chemo (SC) vs Systemic chemo alone:
  - Significant benefit in median survival\(^2\)

- Chemo refractory pts SIRT+SC vs SC alone:
  - Significantly longer median time to liver progression\(^3\)
  - High percentage or partial response and stable disease with significantly longer median survival amongst responders\(^4\)

---

1 Gray B. et al, Ann Oncology, 2001  
2 Van Hazel G. et al, JSO, 2004  
3 Hendlisz A. et al, JCO, 2010  
4 Kennedy AS. Et al, Int J Rad Onc,Bio,Phy, 2006
• No increase incidence of grade 2 and 3 toxicity for SIRT+SCT\(^1,2\)

• Few isolated cases of organ specific damage (radiation hepatitis, liver abscess, biliary ischemic damage)\(^1-3\)

• No evidence of age related side effects

---

\(^1\) Gray B. et al, Ann Oncology, 2001
\(^2\) Hendlisz A. et al, JCO, 2010
\(^3\) Van Hazel G. et al, JSO, 2004
• Tolerability and improvement in survival in elderly patients with oxaliplatin-or irinotecan-based chemotherapy +/- novel biologic agents (bevacizumab) have been demonstrated by several studies\textsuperscript{1-5}

• Elderly patients with good performance status tolerated adjuvant and palliative chemotherapy for CRC as well as for younger patients\textsuperscript{6}

• Following preoperative chemotherapy there is an increase in perioperative morbidity but not mortality\textsuperscript{7}

\textsuperscript{1} Hurwitz H et al, NEJM, 2004
\textsuperscript{2} Grothey A et al, JCO, 2007
\textsuperscript{3} Kozloff M et al, JCO, 2006
\textsuperscript{4} Kretzschmar A et al, Am Soc Clin Onc, 2006
\textsuperscript{5} Van Cutsem E, et al, Am Soc Clin Onc, 2006
\textsuperscript{6} Popescu RA, et al, JCO, 1999
\textsuperscript{7} Adam R. et al, BJS, 2010
LIVER RESECTION

- Hepatic resection remains the treatment of choice for HCC > 2 cm

- The life expectancy of patients with HCC is unaffected by age >70 years\(^1,2\)

- Although the overall application rate of curative or effective treatments is unaffected by age, their distribution differs according to age. Elderly patients are more frequently treated with percutaneous ablation and less frequently with hepatic resections

- Patient survival is unaffected by age in each treatment subgroup

- Balancing benefits and risks of surgical resection, often clinicians are still reluctant to advise in favour of surgical treatment

\(^1\) Mirici-Cappa F. et al, GUT, 2010
\(^2\) Tsukioka G et al, World J Gastr, 2006
LR: SAFETY AND EFFICACY

- In selected elderly pts with controlled comorbidities LR has been proven to be safe\(^1\)\(^2\):
  - Comparable perioperative morbidity
  - Comparable postoperative mortality

- Evidence suggest that elderly pt treated with LR have significant better median survival and OS\(^1\)\(^3\)

1 Huang J et al, J Gastroint Surg, 2009
2 Takenaka K et al, Arch Surg, 1994
3 Mirici-Cappa F et al, GUT, 2010
HCC: RFA

- It is indicated for elderly pts not fit for resection or with single HCC nodule < 2 cm

- It carries same low periprocedure complications rate as for younger pts\(^1,2\)

- Comparable median survival\(^3\), OS and DFS\(^1\)

---

1 Takahashi H et al, Hep Research, 2010  
2 Benevento et al, XXIII Meeting of Italian Soc of Geriatric Onc, 2010  
3 Mirici-Cappa F. et al, GUT, 2010
It is indicated for
- inoperable,
- non ablatable,
- locally advanced uni or multifocal HCC

Controindications:
- Child’s C
- PV thrombosis
- Extrahepatic disease

Chemotherapeutic agents alone or in combination:
- Doxorubicin
- Cisplatin
- Mitomycin C
• Similar hepatic and systemic toxicity for young and elderly pts\textsuperscript{1,2}

• Comparable TACE-related mortality (3-4%)\textsuperscript{1,2}

• Comparable:
  • overall median survival\textsuperscript{3}
  • disease-specific survival\textsuperscript{3}
  • OS\textsuperscript{1}

\textsuperscript{1} Takahashi H et al, Hep Research, 2010
\textsuperscript{2} Benevento et al, XXIII Meeting of Italian Soc of Geriatric Onc, 2010
\textsuperscript{3} Mirici-Cappa F. et al, GUT, 2010
TACE with DRUG-ELUTING BEAD

- DC Bead: drug delivery embolization system, comprising biocompatible, nonreabsorbable hydrogel beads capable of being loaded doxorubicin
- Advantages:
  - Enhance tumor drug delivery
  - Reduce systemic availability
• Higher rate (p=0.11) of:
  • Complete response
  • Objective response (complete response + partial response)
  • Disease control (objective response + stable disease)

• Significant increase in objective response:
  • Child B pts
  • Bilobar disease
  • Recurrent disease

• Significant reduction in:
  • Liver toxicity
  • Doxorubicin-related side effects

• Significant improvement:
  • Median survival
  • Overall survival

1 Lammer J et al, Cardiovasc Intervent Radiol, 2010
2 Dhanasekaran R et al, J Surg Onc, 2010
INDICATIONS AND FUTURE PROSPECTS

- Same as cTACE
- Pts with advance background liver disease
- Pts with systemic comorbidities (elderly)
- Possible combination with Sorafenib:
  - RCT SPACE: comparing DC Bead TACE plus placebo versus DC Bead TACE plus sorafenib.
Liver resection remains the only available treatment to potentially achieve long term survival for Hilar and Intrahepatic CC.

- Evidence suggests that:
  - No difference in perioperative morbidity and mortality
  - Longer in hospital stay
  - Similar2 or favourable long term outcomes1
• Dedicated preoperative assessment

• Tumor biological characterization

• Postoperative enhance recovery programs

• Use of selective drug delivery devices

• Multimodality approach to treatments that combine systemic treatment with surgical and interventional procedure

• Dedicated share database
We strongly recommend considering senior patients for active aggressive treatment whenever possible!