Current status of treatment strategies in the management of colorectal cancer

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Overall 5-year survival CRCa

http://info.cancerresearchuk.org/cancerstats/
Management of CRC: A multidisciplinary team approach

- Endoscopist
- Oncologist
- Pathologist
- Colorectal Surgeon
- Radiologist
- Hepatic/thoracic surgeon
Strategies for managing CRCa

- Surgical resection
- Chemotherapy
- Radiotherapy
- Tissue ablation
- Liver directed therapy
Strategies for managing CRCa

- Surgical resection
- Chemotherapy
- Radiotherapy
- Tissue ablation
- Liver directed therapy
Resection of colonic primary: contemporary view

- Principal of achieving R0 resection imperative
- Greater emphasis placed on restoring enteric continuity
- Importance of adequate nodal sampling (>12)
- Dramatic increase in laparoscopic-assisted colectomy (LAC) over last decade
- Randomized trials and meta-analyses have identified no detrimental impact on recurrence or survival for LAC
In the largest trial, the United States Intergroup Clinical Outcomes of Surgical Therapy (COST) trial, 872 patients with colonic adenocarcinoma were assigned to OC or LAC

- Operative time was significantly longer with LAC (150 versus 95 minutes)
- 21 percent of laparoscopic cases required conversion to an open
- LAC group had modestly reduction in hospital stay (five versus six days) and parenteral analgesic use (three versus four days).

For patients who have undergone potentially curative resection of a colon cancer, the goal of postoperative (adjuvant) chemotherapy is to eradicate micrometastases

- 30% reduction in the risk of disease recurrence
- Benefits most clearly demonstrated in stage III (node-positive) disease
- Typically oxaliplatin based regimen in combination with 5-FU
- Commencing 6-8 weeks post-op for 6 months duration
Resection of CRCa liver metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Last Year Included</th>
<th>Span, Years</th>
<th>Patients, N</th>
<th>5-Year OS, %</th>
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<td>Fernandez</td>
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<td>Pawlik*</td>
<td>2004</td>
<td>14</td>
<td>557</td>
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<td>Adam*</td>
<td>2004</td>
<td>30</td>
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<td>Figueras</td>
<td>2004</td>
<td>14</td>
<td>501</td>
<td>45</td>
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</table>

*Patients included from multiple institutions (vs single-institution series).
Survival after hepatic resection has improved over time

- Lower operative mortality
  - ~1% with experienced hepatobiliary surgeons
- Improved patient selection
  - CT, MRI, PET, PET/CT
- Improved surgical techniques
  - IOUS, PVE, RFA
- More frequent and better perioperative chemotherapy
  - Irinotecan, oxaliplatin, biologics
- Increased rates of repeat hepatectomy following recurrence
CRCa pulmonary metastases

- 2nd most frequent site for metastases
- 5-10% synchronous liver and lung metastases
- Treatment by resection or ablation
- 5-year survival approx 30%

- Poor prognostic factors
  - Bilateral disease
  - >3 metastases
  - >3cm maximum diameter
  - Hilar adenopathy
Management of metastatic colorectal cancer

- Simultaneous bowel and metastases
- Metastectomy after CRCa primary
- CRCa primary after metastectomy
- Chemotherapy prior to either resection
Management of metastatic colorectal cancer

- Simultaneous bowel and metastases
- Metastectomy after CRCa primary
- CRCa primary after metastectomy
- Chemotherapy prior to either resection

*Order does not appear to be important – just need to receive combination of both surgery and chemotherapy*
131 patients with colorectal metastases received preoperative chemotherapy

Tumour better but liver worse!

Not observed <6 cycles

Bilchik, et al., J Clin Oncol 2005; 23:9073
Complete response of CRCa liver metastases

Complete radiological response
n=66

Intra-operative exploration
(liver examination and IOUS)

No macroscopic residual disease
N=46 metastases

Resection of site of initial 15 metastases

Viable tumour cells 12/15

31 sites of initial metastases left
In situ 1-year follow up

No recurrence in situ 8/31 metastases

Recurrence in situ 23/31 metastases

55/66 (83%) persistent disease or early recurrence

Radiological response: Viable cells at periphery
Reality for most patients

Disease is initially beyond resectability
Strategies to improve resectability

1. Reduce size index lesion remnant
2. Increase size future liver
3. Chemotherapy
4. Targeted ablation
5. Liver directed therapy
6. Portal vein embolisation
7. 2-stage hepatectomy
Neoadjuvant Oxaliplatin: Paul Brousse Hospital study

Treated pts, 1988-2003 (N= 2047)

- Initially nonresectable 74% (n= 1512)
- Initially resectable 26% (n= 535)

Chemotherapy (n=1512)

- Nonresectable 86% (n=1307)
- Converted to resectable 14% (n=205)

Resection (n=740)

- Initially resectable 72% (n=535)
- Converted to resectable 28% (n=205)

Outcomes (N= 2047)

- No resection 64% (n=1307)
- Resection after chemotherapy 10% (n=205)
- Resection 26% (n=535)

Survival of Liver Metastases based on initial resectability

Initially nonresectable (n = 95)
Resectable (n = 425)

Survival Time (Yrs)

Patients Surviving (%)

Resectable (n = 425)
Initially nonresectable (n = 95)
Liver directed therapies

Catheter placement

Hepatic artery

Portal vein
Irinotecan loaded Microspheres (DEBIRI TACE)

- Catheter minimally invasive
- Polyvinyl alcohol microspheres
- Ischaemia and drug delivery
- Single treatment event
- No systemic effects
**Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>3-months</th>
<th>6-months</th>
<th>12-months</th>
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<tbody>
<tr>
<td>Complete</td>
<td>8</td>
<td>9</td>
<td>12</td>
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<tr>
<td>Partial</td>
<td>35</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Stable</td>
<td>19</td>
<td>30</td>
<td>36</td>
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<tr>
<td>Progression</td>
<td>3</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

*Compared to best supportive care, RR 2-5% at 3-6 months*
Radio-embolisation (SIRT)

- Yttrium-90 is a beta emitter with $t_{1/2}$ 64 hours
- Maximum range of penetration 11mm (mean 2.5m)
- Normal liver poor tolerance to DXR
- Blood supply of liver tumors almost entirely arterial
- Able to administer selectively by a minimally invasive technique
RCT SIR-Spheres + 5FU/LV first line

- First line treatment n=21 patients with hepatic CRCa metastases
- 24% extra-hepatic disease
- TTP 18.6 vs 3.6 months (p<0.0005)
- Greater number of G3-4 toxicities with SIRT
- Improvement in QoL at 3-months

### First line treatment hepatic CRCa metastases

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>Cohort</th>
<th>ORR</th>
<th>SD</th>
<th>Median TTP(^a) or PFS(^b)</th>
<th>Median Survival</th>
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<tbody>
<tr>
<td><strong>First-Line</strong></td>
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<tr>
<td>Gray(^1)</td>
<td>74</td>
<td>SIR-Spheres(^+) + FUdR HAC</td>
<td>LO</td>
<td>44(^\text{w})</td>
<td>8.3%</td>
<td>15.9 months(^\text{AL})</td>
<td>39% at 2 yr</td>
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<tr>
<td></td>
<td></td>
<td>vs. FUdR HAC</td>
<td>LO</td>
<td>18(^\text{w})</td>
<td>38.2%</td>
<td>9.7 months(^\text{AL})</td>
<td>29% at 2 yr</td>
</tr>
<tr>
<td>van Hazel(^2)</td>
<td>21</td>
<td>SIR-Spheres(^+) + 5FU/LV</td>
<td>LD</td>
<td>90.1(^\text{F})</td>
<td>9.9%</td>
<td>18.6 months(^\text{AL})</td>
<td>29.4 months</td>
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<tr>
<td></td>
<td></td>
<td>vs. 5FU/LV</td>
<td>LD</td>
<td>0%</td>
<td>60.0%</td>
<td>3.6 months(^\text{AL})</td>
<td>12.8 months</td>
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<tr>
<td>Sharma(^4)</td>
<td>20</td>
<td>SIR-Spheres(^+) + FOLFOX4</td>
<td>LD</td>
<td>90%</td>
<td>10%</td>
<td>9.3 months(^\text{AL})</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LO</td>
<td></td>
<td></td>
<td>14.2 months(^\text{AL})</td>
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<td>Kosmider(^5)</td>
<td>19</td>
<td>SIR-Spheres(^+) + FOLFOX4 or 5FU/LV</td>
<td>LD</td>
<td>84%</td>
<td>5%</td>
<td>10.4 months(^\text{AL})</td>
<td>29.4 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LO</td>
<td></td>
<td></td>
<td>10.7 months(^\text{AL})</td>
<td>37.8 months</td>
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<tr>
<td>Tie(^6)</td>
<td>31</td>
<td>SIR-Spheres(^+) + FOLFOX4 or 5FU/LV</td>
<td>LO</td>
<td>91%</td>
<td>9%</td>
<td>13.2 months(^\text{AL})</td>
<td>30.7 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LO</td>
<td></td>
<td></td>
<td>16.4 months(^\text{AL})</td>
<td></td>
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<tr>
<td>phase II/III studies</td>
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<td>FOLFOX4(^7)-(^10)</td>
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<td>32–59%</td>
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<td>7.6–9.0 months(^\text{AL})</td>
<td>16.2–19.5 months</td>
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</table>
Salvage therapy of treatment refractory disease

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>Cohort</th>
<th>ORR</th>
<th>SD</th>
<th>Median TTP(^{\text{AL}}) or PFS(^{\text{AL}})</th>
<th>Median Survival</th>
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</thead>
<tbody>
<tr>
<td>Hendlisz(^{27})</td>
<td>44</td>
<td>SIR-Spheres(^{+}) + 5FU vs. 5FU ( &gt; SIR-Spheres(^{+}) at PD)</td>
<td>LO</td>
<td>10%</td>
<td>76%</td>
<td>5.5 months(^{\text{AL}})</td>
<td>10.0 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LO</td>
<td>0%</td>
<td>35%</td>
<td>2.1 months(^{\text{AL}})</td>
<td>7.3 months</td>
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<tr>
<td>Seidensticker(^{29})</td>
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<td>SIR-Spheres(^{+}) vs. BSC matched pairs</td>
<td>LD</td>
<td>41.4%</td>
<td>17.2%</td>
<td>5.5 months(^{t})</td>
<td>11.9 months</td>
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<tr>
<td></td>
<td>29</td>
<td>SIR-Spheres(^{+}) vs. conventional therapy or BSC</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>2.1 months(^{t})</td>
<td>6.6 months</td>
</tr>
<tr>
<td>Cosimelli(^{30})</td>
<td>50</td>
<td>SIR-Spheres(^{+})</td>
<td>LD</td>
<td>24%</td>
<td>24%</td>
<td>4 months(^{t})</td>
<td>12.6 months</td>
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<td>Sofocleous(^{31})</td>
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<td>SIR-Spheres(^{+})</td>
<td>LD</td>
<td>70.6%(^{\text{DCR}})</td>
<td>6 months(^{t})</td>
<td>16.0 months</td>
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<td>Kennedy(^{32})</td>
<td>606(^{5})</td>
<td>SIR-Spheres(^{+})</td>
<td>LD</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>9.6 months</td>
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<tr>
<td>Sofocleous(^{33})</td>
<td>18(^{5})</td>
<td>SIR-Spheres(^{+})</td>
<td>LD</td>
<td>40.0%(^{\text{DCR}})</td>
<td>5.1 months(^{t})</td>
<td>7.4 months</td>
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<td>Leoni(^{34})</td>
<td>51(^{5})</td>
<td>SIR-Spheres(^{+})</td>
<td>LD</td>
<td>24%</td>
<td>24%</td>
<td>nr</td>
<td>8.0 months</td>
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<td>Nace(^{35})</td>
<td>51(^{5})</td>
<td>SIR-Spheres(^{+}) (+ FUDR HAC)(^{33\text{a}})</td>
<td>LD</td>
<td>12.9%</td>
<td>64.5%</td>
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<td>17.0 months</td>
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<td>Clanni(^{36})</td>
<td>41(^{5})</td>
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<td>46%</td>
<td>36%</td>
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<td>Jakobs(^{37})</td>
<td>41(^{5})</td>
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<td>17%</td>
<td>61%</td>
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<td>10.5 months</td>
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<td>Kennedy(^{38})</td>
<td>208(^{5})</td>
<td>SIR-Spheres(^{+}) responders vs. non-responders &amp; historical controls</td>
<td>LD</td>
<td>35.5%(^{\text{w}})</td>
<td>55%</td>
<td>nr</td>
<td>10.5 months</td>
</tr>
</tbody>
</table>

\(^{\text{AL}}\) = alive; \(^{t}\) = time; \(^{\text{DCR}}\) = disease control rate; \(^{\text{w}}\) = with; \(^{\text{ns}}\) = not significant; \(^{\text{P}}\) = p-value
Chemo-refractory liver dominant disease

Appears to be a clear benefit in survival for unresectable, heavily pre-treated CRCa liver metastases
Local ablative therapies

- Percutaneous ethanol injection (PEI)
- Cryotherapy
- Microwave coagulation therapy (MCT)
- Laser induced thermotherapy (LITT)
- Electrolysis
- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)
Radiofrequency ablation of CRCa liver metastases

- Systematic review\(^1\) 2 comparative studies, 11 case series
- Post procedure complication rate 0-33%
- Shorter survival than surgical resection
- Local recurrence rate 4-55%

<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>Resection</th>
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<tbody>
<tr>
<td>Survival (months)</td>
<td>44 (median)</td>
<td>54 (mean)</td>
</tr>
<tr>
<td>5-year survival (%)</td>
<td>40</td>
<td>53</td>
</tr>
</tbody>
</table>

For lesions <3 cm, RFA and resection probably equivalent\(^2\)

\(^1\)Sutherland et al., Arch Surg 2006; 141:181-90
\(^2\)Mulier S et al., Dig Surg 2009; 25(6):445
Microwave ablation of liver tumours

- MWA zones larger than for RFA
- Local vessels caused less deflection
- No pathological difference in degree of necrosis
- (Lower recurrence rates)
Summary: An evolving paradigm

The Past 2000

- Not resectable (80-90%)

The Present 2013

- Resectable (30-40%) 55%
- Not resectable (30-55%)

Overall summary

- Principals in the management of the primary cancer are unchanged – method become less invasive
  - Definition of resectability of has changed – metastatic disease no longer a contraindication
  - Chemotherapy does improve long-term outcome (neo-adjuvant, adjuvant)
  - Risks of prolonged systemic therapy must be weighed against benefits
  - Liver targeted therapies (DEBIRI, SIRT) appear to offer survival benefit, but need to better define treatment group
  - Minimally invasive tissue ablation complements resection
  - Individualized, multidisciplinary approach required to optimize outcomes