Recent therapeutic advances for Colorectal Cancer

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# Epidemiology of colorectal cancer in Europe

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Male incidence</th>
<th>Female incidence</th>
<th>Approximate 5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to bowel wall</td>
<td>9,979</td>
<td>9,497</td>
<td>85% to &gt;90%</td>
</tr>
<tr>
<td>II</td>
<td>Bowel wall penetration</td>
<td>31,184</td>
<td>29,680</td>
<td>70% to 80%</td>
</tr>
<tr>
<td>III</td>
<td>Lymph node involvement</td>
<td>43,658</td>
<td>41,552</td>
<td>25% to 60%</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
<td>39,916</td>
<td>37,992</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Data from 1990-1994
Globocan 2000, Eurocare-3, 2003
Challenges

• Common
• Late presentation
• High relapse rate after apparently curative surgery
• Poor survival with metastases
Opportunities

- Screening does reduce mortality and a programme has been announced in UK
- Active simple agents available for chemoprevention: aspirin prevents polyps!
- Better MDT collaboration improves outcomes
- Adjuvant therapy increases survival
- More effective systemic therapy is coming
Developments in colorectal cancer

- Multidisciplinary management of rectal cancer
- A new paradigm in the management of advanced disease
Multidisciplinary Management of Rectal Cancer

- **Pathology**: definition of the circumferential resection margin
- **Surgery**: total mesorectal excision
- **Radiology**: MRI pre-operative staging to define tumour at the CRM
- **Radiotherapy**: selective pre-operative strategy
- **Chemotherapy**: combinations; pre/post op
the mesorectal fascia
Tumour spread confined within the Mesorectal fascia
The Circumferential Resection Margin

CRM +ve ≤1mm
Plane of surgery: MRC CR07 (n=1119)

<table>
<thead>
<tr>
<th>Plane of excision</th>
<th>Mesorectal</th>
<th>Intra-mesorectal</th>
<th>Muscularis propria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>53%</td>
<td>34%</td>
<td>13%</td>
</tr>
<tr>
<td>CRM +ve</td>
<td>9%</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>Local rec</td>
<td>4%</td>
<td>8%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Total mesorectal excision

R.J. Heald et al., Lancet 1986/93: local recurrence rate < 5%
MRI scan for pre-operative staging

MRI defined criteria for tumour staging

- Extramural spread
- Circumferential resection margin
- Lymph node status

- **Favourable:** T1, 2, 3a, N0
- **Unfavourable:** T3>1mm, N+
- **Advanced:** T4, CRM < 1mm
Primary endpoint: MRI = surgery @ 0.05cm
Result: mean difference = 0.04606 cm

Prediction: 219/295 predicted to be CRM –ve
Result: 13/219 CRM +ve (5.9%)
Accuracy: CRM @ 1mm: 266/325
@ 2mm: 200/325
Nodal involvement on MRI

Assessment of nodal involvement on MRI is unpredictable. USPio contrast agent is taken up by normal nodes and improves prediction.
Controversies: lower third cancers

- Low tumours < 6cm
- 87/282 (33%) CRM +ve
- Which lower third tumours need pre-op RT?
  - Full thickness T2, all T3, T4
  - need EUS + MRI to define
- Little benefit from short course (10.5 v 11.9%)
- Therefore should have long course!

Angled high resolution MRI
Conclusion

• MRI is able to segregate a group of high risk rectal cancer patients with cancer within 1mm of mesorectal fascia, who have a higher local recurrence rate and greater risk of death.

• Outcomes in low and intermediate risk groups are similar.
Radiotherapy in rectal cancer

• Three schedules have shown equivalent effectiveness in reduction in local recurrence:
  – Short course pre-operative radiotherapy (1 wk)
  – Pre-operative Chemoradiotherapy (5 wks with 5FU)
  – Pre-operative radiotherapy plus post operative adjuvant chemotherapy
Is pre operative RT better than post-op? Pre-op v post-op chemoradiotherapy for rectal cancer.

- T3/ T4 or N+ ca rectum
- Pre-op 5040cGy/28# + 5FU 1g/m²/d over 4 days week 1 and 5. Surgery at 6 weeks. Post op adjuvant 5FU 4 cycles
- Post-op: same plus boost of 540cGy

Sauer et al, NEJM 2004; 351, 1731-40
## Results

<table>
<thead>
<tr>
<th></th>
<th>Pre-op CRT</th>
<th>Post-op CRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>421</td>
<td>402</td>
<td></td>
</tr>
<tr>
<td>5 yr OS</td>
<td>76%</td>
<td>74%</td>
<td>0.80</td>
</tr>
<tr>
<td>Local relapse</td>
<td>6%</td>
<td>13%</td>
<td>0.006</td>
</tr>
<tr>
<td>Grade 3 &amp; 4 acute toxicity</td>
<td>27%</td>
<td>40%</td>
<td>0.001</td>
</tr>
<tr>
<td>Grade 3 &amp; 4 chronic toxicity</td>
<td>14%</td>
<td>24%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Sauer et al, NEJM 2004; 351, 1731-40
# MRC CR07: 3 year LR by plane of surgery and treatment arm

<table>
<thead>
<tr>
<th>Plane of surgery</th>
<th>PRE</th>
<th>POST</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesorectal Plane</td>
<td>1%</td>
<td>6%</td>
<td>4.47 (1.94,10.32)</td>
</tr>
<tr>
<td>Intramesorectal plane</td>
<td>4%</td>
<td>10%</td>
<td>2.02 (0.87,4.66)</td>
</tr>
<tr>
<td>Muscularis propria plane</td>
<td>9%</td>
<td>19%</td>
<td>2.76 (1.02,7.41)</td>
</tr>
</tbody>
</table>

Quirke et al, ASCO 2006
### Long term complications of short course pre op RT in Swedish studies

| Event                                | Radiotherapy (n = 65) | No radiotherapy (n = 74) | P
|--------------------------------------|-----------------------|--------------------------|---
| Any adverse event                    | 45 (69)               | 32 (43)                  | 0.002
| Cardiovascular disease               | 23 (35)               | 14 (19)                  | 0.032
| Venous thromboembolism               | 4 (6)                 | 5 (7)                    | 0.823
| Faecal incontinence*                 | 12 (57)               | 11 (26)                  | 0.013
| Small bowel obstruction              | 19 (29)               | 13 (18)                  | 0.074
| Urinary incontinence                 | 29 (45)               | 20 (27)                  | 0.023
| Incomplete bladder emptying          | 17 (26)               | 13 (18)                  | 0.193
| Fractures (all types)                | 11 (17)               | 6 (8)                    | 0.118
| Hip and pelvic fractures             | 3 (5)                 | 1 (1)                    | 0.227

*Pollack et al, British Journal of Surgery 2006; 93: 1519–1525*
I consider the need to use post-operative radiotherapy a failure of multidisciplinary team working

Poor staging
Poor surgery
Poor decision making
Pre-operative chemoradiation no longer just 5FU

- 5FU/FA (Bossett) or C.I 5FU
- 5FU/FA + Oxaliplatin (FORTE, ASCO 2002)
- 5FU/FA + Irinotecan (Descartes, ASCO 05)
- Capecitabine
- Capecitabine + Oxaliplatin (Socrates ASCO 04, 05)
- Capecitabine + cetuximab (XERXES)
## Cardiff Clinical Protocol for Rectal Cancer

<table>
<thead>
<tr>
<th>MRI scan / height above anal verge</th>
<th>Good T1, 2, 3a, N0</th>
<th>Bad T3&gt;1mm, or N+</th>
<th>Ugly T4, CRM &lt; 2 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5cm (APER likely)</td>
<td>T1, T2*, N0</td>
<td>N/A</td>
<td>Ft T2*, T3, T4, Nx</td>
</tr>
<tr>
<td></td>
<td>Surgery only</td>
<td></td>
<td>Long course CTRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ surgery @ 6/52</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>T1, T2, T3a N0</td>
<td>T3b+, N1-3,</td>
<td>T4, CRM threatened</td>
</tr>
<tr>
<td></td>
<td>Surgery only</td>
<td>Short course RT</td>
<td>Long course CTRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Surgery @ 1/52</td>
<td>+ surgery @ 6/52</td>
</tr>
</tbody>
</table>
A new paradigm in the management of advanced colorectal cancer

Not all patients with metastases are incurable
Curative and palliative therapy: strategies in cancer treatment

Survival vs. Time

- Palliative therapy
- Curative therapy
Survival after liver resection of colorectal metastases
Paul Brousse Hospital
473 patients (April 1988–July 1999)

Resectable: 335
Initially non-resectable: 138

p=0.01

Resection rate of metastases and tumor response

- **Studies including selected patients** (liver metastases only, no extrahepatic disease) 
  \( r=0.96, \ p=0.002 \)

- **Studies including all patients** with mCRC (solid line) 
  \( r=0.74, \ p=0.001 \)

- **Phase III studies** in mCRC (dashed line) 
  \( r=0.67, \ p=0.024 \)

First line chemotherapy in CRC: benefit and evolution

Response Rate (%) & Median Survival (months)

BSC bolus 5-FU 5-FU/FA Mayo 5-FU/FA inf. FOLFOX-6 FOLFIRI IFL Bev

New agents in colorectal cancer

Fluoropyrimidines

OXALIPLATIN / IRINOTECAN

BEVACIZUMAB

1. Tumor secretes VEGF
2. VEGF increases endothelial protease expression
3. Endothelial cell migration and proliferation promoted by VEGF
4. Microvascular networking promoted by VEGF

CETUXIMAB

EGFR Mab
Cetuximab prospective studies in non-resectable liver metastases — non-selected patients from Phase II studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>RR</th>
<th>Resection</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIO/IRI + Cetuximab</td>
<td>21</td>
<td>68%</td>
<td>24% *</td>
<td>Folprecht</td>
</tr>
<tr>
<td>FOLFOX + Cetuximab</td>
<td>43</td>
<td>81%</td>
<td>21%</td>
<td>Diaz-Rubio</td>
</tr>
<tr>
<td>FOLFIRI + Cetuximab</td>
<td>40</td>
<td>43%</td>
<td>13%</td>
<td>Rougier</td>
</tr>
</tbody>
</table>

Does cetuximab improve the response rate in addition to Oxaliplatin + 5FU and therefore the resection rate in patients with potentially resectable liver metastases?

New Epoch trial and EORTC trial open

* Resectability rate = 24%, resection rate = 21% (1 pt. declined resection)
Resectability – Irresectability

Potentially resectable

⇒ resectable
  Standard resection
  (> 40% residual vol.)
  Extended resection
  (< 40% residual vol.)

⇒ irresectable
  > 6 segments
  > 70% volume
  All 3 liver veins

OncoSurge Model 2004
Influence of Neoadjuvant Chemotherapy on the Liver and Liver function before/after resection
Not all patients with metastases are incurable

• Select patients for a potentially curative strategy who have
  – A resectable primary and
  – Metastatic disease limited to liver (+ lungs)
  – Fit for sequential chemotherapy and 2 or more resections

• Patients for palliative chemotherapy with multi-organ metastatic disease:
  – QL and survival are joint aims
Recent therapeutic advances in Colorectal Cancer

• Optimal management of rectal cancer demands multidisciplinary collaboration and evaluation for EVERY patient

• Improvements in systemic therapy are challenging accepted paradigms in the management of metastatic disease