Current chemotherapy and radiotherapy treatments for Colorectal Cancer

Dr Alice Dewdney
Outline

- Adjuvant chemotherapy
- Neoadjuvant radiotherapy

- Metastatic disease
  - Neoadjuvant chemotherapy
  - Liver directed therapies
  - Palliative chemotherapy
Colorectal cancer is common

Total 73,039 cases 2008 (24% of all cancers)

Source: http://info.cancerresearchuk.org/cancerstats/incidence/commoncancers/
Survival from cancer is improving over time

5 year relative survival rate, colon cancer, 1971-2006

5 year survival for colon cancer has doubled in the past 30 years

Source: http://info.cancerresearchuk.org/cancerstats/types
Multidisciplinary collaboration and research leads to improved outcomes for cancer patients

- Imaging: CT/MRI/PET
- Radiation Therapy
- Surgery
- Drug Therapy
- Clinical Trials
- Targeted therapy
- Chemotherapy
How do we manage colorectal cancer?

**COLON**
- Staging
- MDT
- Surgery
- +/- Adjuvant chemotherapy

**RECTUM**
- Staging
- MDT
- +/- Neoadjuvant radiotherapy
  - short course
  - long course CRT
- Surgery
- +/- adjuvant chemotherapy
TNM staging colon cancer
Dukes/TNM

A (stage I)  T1N0M0

B (stage II)  T1,T2,T3, T4 N0,M0

C (stage III)  T1,T2, N1,M0
               T3,T4 N1, M0, Any T N2,M0

D (stage IV)  Any T, any N, M1
Surgery - colonic tumours

Depends on site of tumour;

- Right hemicolecctiony
- Left hemicolecctiony
- Sigmoid colectomy
Who needs adjuvant chemotherapy?

**High risk Dukes B**

1. emergency presentation with obstruction or perforation
2. evidence of extramural venous invasion (EMVI)
3. T4 tumours
4. poor lymph node yield (<8 retrieved)

**Dukes C**

- 6 months FOLFOX/XELOX **or** capecitabine*
  - *8% benefit capecitabine
  - **12-14% benefit with addition of oxaliplatin

**6 months Capecitabine***
- **2-4% benefit**
What about the elderly?

• > 70 yrs not very good evidence for combination treatment so if fit capecitabine only
Can we predict who might benefit?

- Deficient mismatch repair (dMMR)
- Or microsatellite instability (MSI)/MSI-high
- 15% of CRC
# Mismatch repair

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-yr recurrence-free rate</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
<th>5-yr survival rate</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>dMMR</td>
<td>pMMR</td>
<td></td>
<td></td>
<td>dMMR</td>
<td>pMMR</td>
<td></td>
<td></td>
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<tr>
<td>Stage II</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>89%</td>
<td>74%</td>
<td>0.27</td>
<td>0.10 - 0.75</td>
<td>0.12</td>
<td>90%</td>
<td>78%</td>
<td>0.27</td>
</tr>
<tr>
<td>5FU-mrx (n=1155)</td>
<td>88%</td>
<td>83%</td>
<td>0.81</td>
<td>0.55 - 1.19</td>
<td>0.295</td>
<td>88%</td>
<td>87%</td>
<td>0.67</td>
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<tr>
<td>Stage III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>60%</td>
<td>47%</td>
<td>0.59</td>
<td>0.28 - 1.23</td>
<td>0.162</td>
<td>59%</td>
<td>54%</td>
<td>0.69</td>
</tr>
<tr>
<td>5FU-mrx (n=2723)</td>
<td>72%</td>
<td>64%</td>
<td>0.80</td>
<td>0.66 - 0.97</td>
<td>0.025</td>
<td>77%</td>
<td>71%</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Can we predict who might benefit?
MMR testing

Test all stage II CRC with any high risk feature

- EMVI
- Obstruction/performation
- T4
- Poorly differentiated

- Histopathologists to identify cases locally and send to STH for IHC prior to MDT
- Information used to make decisions about use of adjuvant capecitabine
Neoadjuvant chemotherapy - FOXTROT

Patient is eligible for FOXTROT & agrees to take part: if KRAS-wt allocate to one of three treatment groups

A

OxMdG x 6 weeks

Surgery

OxMdG x 18 wks
(or, optionally, 6 wks)

B

OxMdG plus panitumumab x 6 weeks

Surgery

OxMdG x 18 wks
(or, optionally, 6 wks)

C

Surgery

OxMdG x 24 wks
(or, optionally, 12 wks)
Practicalities - FOLFOX

- Via a PICC line
- Need a family member to be trained to disconnect and flush line once a week
- Seen and assessed before each cycle
- Oxaliplatin given on day unit then 5FU pumped fitted 46hrs.
- Every 2 weeks
Practicalities XELOX

• Oxaliplatin given via cannula on day unit
• Capecitabine – BD 14 days, 3 weekly
• Paracetamol sized tablets usually 3-4 at at time
Side effects of treatment

Aim of treatment important in assessing side effects

- Palliative intent – tolerate less side effects
- Adjuvant/potentially curative – tolerate more
Potential side effects chemotherapy

- Neutropenia/infection risk
- **Oxaliplatin – cold induced pins & needles/peripheral neuropathy
- Nausea and vomiting
- Diarrhoea
- Hand and foot syndrome (PPE)
- Chest pain
- Fatigue
- DVT
The rectum

Usually defined as 10-15 cm above anal verge
Type of surgery

Depends on location of tumour:
• Anterior resection
• Low anterior resection
• Ultra low anterior resection
• APER
TME surgery

Total mesorectal excision

Removal of mesorectum and draining lymph nodes intact

Heald et al 1986
Total mesorectal excision

Heald et al 1986
Which rectal cancers need neoadjuvant treatment?
Defining rectal cancer

- The good
- The bad
- The ugly
How do we characterise?

EMVI +

T3d

+CRM

+CRM
T3 sub staging - rectal ca

<table>
<thead>
<tr>
<th>T3</th>
<th>Tumor invades subserosa through MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3a</td>
<td>Tumor extends &lt;1mm beyond MP</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor extends ≥1-5mm beyond MP</td>
</tr>
<tr>
<td>T3c</td>
<td>Tumor extends &gt;5-15mm beyond MP</td>
</tr>
<tr>
<td>T3d</td>
<td>Tumor extends &gt;15mm beyond MP</td>
</tr>
</tbody>
</table>
Circumferential resection margin (CRM)

The shortest distance from the tumour or lymph nodes to the mesorectal fascia is called circumferential resection margin.

Why is it important?

Local recurrence rates
66% vs. 8%

5YSR
24% vs. 74%
MRI and the CRM
So what do we actually do?

- Radiotherapy reduces local recurrence but no impact on OS
- Issue of long term toxicity
- So who should we give it to?
- Stratify according to risk
**NICE guidelines**

| High | • A threatened (< 1 mm) or breached resection margin or  
|      | • Low tumours encroaching onto the inter-sphincteric plane or with levator involvement |
| Moderate | • Any cT3b or greater, in which the potential surgical margin is not threatened or  
|      | • Any suspicious lymph node not threatening the surgical resection margin or  
|      | • The presence of extramural vascular invasion[^1] |
| Low | • cT1 or cT2 or cT3a and  
|      | • No lymph node involvement |

[^1] This feature is also associated with high risk of systemic recurrence.

- Low risk (the good) – surgery
- Intermediate risk (the bad) – SCRT
- Intermediate/borderline and High Risk (the ugly) - CRT
Pre treatment

- ?defunctioning
- Any risk factors for capecitabine
Radiotherapy planning

- Patient immobilised
- Tattoos
- CT scan with IV contrast
- CT planned
- Verification
- Consent
GTV
CTV-A
CTV-B
CTV-F
PTV
Treatment plan
Practicalities of treatment

Short Course
- 25Gy/5#
- Mon-fri
- Surgery week afterwards

Long course
- 45Gy/25#
- Mon-fri 5 weeks
- Capecitabine 900mg/m2 PO BD on RT days
- 6-8 week before restaging CT/MRI
Rapid Arc/IMRT
Can we intensify CRT? - Aristotle trial

MRI defined locally advanced rectal cancer
No metastases

Declare proposed post-op chemotherapy policy

N=920

Capecitabine CRT
(Cape 900mg/m2 5 days/week)

SURGERY (8-10 weeks)

Proposed post-op policy

Irinotecan Capecitabine CRT
(Capecitabine 650mg/m2 5d/wk
Irinotecan 60mg/m2 wk 1-4)

SURGERY (8-10 weeks)

Proposed post-op policy

Primary end point – Disease Free survival n=920
Adjuvant chemotherapy for rectal cancer

- Not great evidence
- Mostly extrapolated from colon cancer
- Reasonable for high risk disease
BUT ………

- Liver mets present in 15-25% at presentation
- At up to 50% of patients will develop liver mets during course of disease
Metastatic CRC

1. Patients with isolated/resectable disease
2. Patients with “potentially” resectable disease
3. Patients with never resectable disease
Resectable disease

- Size and number of metastases
- Number of segments involved
- Position in relation to main vessels
- Presence of extra-hepatic disease
Aim of liver resection

• Remove macroscopic disease
• Ro resection
• Leave approximately one third of the standard liver volume, or the equivalent of a minimum of two segments
Resectable disease

- Only 15-20% suitable for resection at presentation
- Up to 50% (30-50%) 5-year overall survival (OS) if patients are carefully selected for resection
- BUT
  - ~70% recurrence rate
  - median time to recurrence 10 months
Synchronous presentation

- Diagnosed with mets at same time as primary lesion
- MRI liver and PET scan to exclude extra-hepatic disease
- Usually operate on primary 1st then neoadjuvant chemotherapy
  - 3 months pre and 3 months post
- Neo-adjuvant chemotherapy allows systemic control to be gained and tests tumour sensitivity to chemotherapy
Metachronous presentation

- Long disease-free interval (e.g. >12 months):
  - consider up-front surgery +/- adjuvant chemotherapy

- Shorter disease-free intervals:
  - systemic control before surgery may be beneficial
“Potentially” Resectable Liver Metastases

- <25% of patients
- Outcome better in patients who become resectable after conversion chemotherapy than in those treated with chemotherapy alone but not as good as in patients with resectable disease at presentation
- Reported resection rates 5-30%
- 5-year OS 33-50% in patients resected after conversion chemotherapy
Management potentially resectable liver mets

- NICE guidelines for currently inoperable tumours with the intention to downstage – if RAS wild type Cetuximab for 16 weeks in addition to Folfox (or Irinotecan)

- Cetuximab Loading dose 400mg/m² over 120 minutes for the first dose.

- Weekly dose 250mg/m² over 60 minutes thereafter.
Group 3 “Never resectable”
Management

- Palliative chemotherapy
- +/- other local therapies if appropriate
Co-morbidities

- Performance status
- PS 0-2 would consider chemo

- IHD – important for 5FU based drugs
- BUT alternatives
  - Irinotecan single agent
  - Oxaliplatin/raltitrexed
Traditional chemotherapy

"I stopped taking the medicine because I prefer the original disease to the side effects."
Impact of chemotherapy

- Median survival 6-9 months no treatment

<table>
<thead>
<tr>
<th>line</th>
<th>Response rate</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st}</td>
<td>60%</td>
<td>6-9 months</td>
<td>18-26m</td>
</tr>
<tr>
<td>2\textsuperscript{nd} line</td>
<td>20%</td>
<td>4-5 months</td>
<td>10m</td>
</tr>
<tr>
<td>3\textsuperscript{rd} line</td>
<td>40% (10% PR/30%SD)</td>
<td>1.8- 2.7m</td>
<td>3-4m</td>
</tr>
</tbody>
</table>

- Median survival 18 months
Shift in treatment paradigms- targeted therapies

More specific to cancer cells → Less damage to normal cells → Fewer side effects for patient

Yap et al Nature Reviews Cancer 2010
Epidermal growth factor pathway

Cetuximab

Panitumumab

EGF

EGFR/HER1

IGF-IR

Ligand binding

Receptor tyrosine kinase domain

HER2

HER3

HER4

VEGFR2

Activation

RAS

PI3K

PTEN

RAF

AKT

MEK

ERK

MTOR

Cell growth and survival

Proliferation
RAS mutations

**RAS FAMILY**

- KRAS
- NRAS
- HRAS
RAS testing

<table>
<thead>
<tr>
<th>Gene</th>
<th>Exon 1</th>
<th>Exon 2</th>
<th>Exon 3</th>
<th>Exon 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td></td>
<td>12 13</td>
<td>61</td>
<td>117 146</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>NRAS</td>
<td></td>
<td>12 13</td>
<td>59 61</td>
<td>117 146</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3%</td>
<td>NT</td>
</tr>
<tr>
<td>BRAF</td>
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<tr>
<td></td>
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</tbody>
</table>

* = codons

Douillard NEJM 2013
Overall Survival in the Updated-Analysis Population

**Hazard ratio, 0.77 (95% CI, 0.64–0.94)**
P = 0.009

**No. at Risk**
- Panitumumab–FOLFOX4: 259, 189, 129, 83, 49, 14
- FOLFOX4 alone: 253, 176, 104, 60, 30, 8

**Events**
- Panitumumab–FOLFOX4: 204/259 (79)
- FOLFOX4 alone: 218/253 (86)

**Median Mo (95% CI)**
- Panitumumab–FOLFOX4: 25.8 (21.7–29.7)
- FOLFOX4 alone: 20.2 (17.6–23.6)
FIRE 3 trial

Heinnemann et al Lancet Oncol 2014
BRAF Mutations

Activation of cell proliferation and survival pathways

- EGF
- EGFR/HER1
- HER2
- HER3
- HER4
- IGF-IR
- VEGFR2

Ligand binding
Receptor tyrosine kinase domain

RAS → PI3K

PTEN

RAF
MEK
ERK

AKT
MTOR

Proliferation
Cell growth and survival
**BRAF mutations - prognostic not predictive**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Panitumumab–FOLFOX4</th>
<th>FOLFOX4 Alone</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>No RAS or BRAF mutations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>228</td>
<td>218</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months of progression-free survival — median (95% CI)</td>
<td>10.8 (9.4–12.4)</td>
<td>9.2 (7.4–9.6)</td>
<td>0.68 (0.54–0.87)</td>
<td>0.002</td>
</tr>
<tr>
<td>Months of overall survival — median (95% CI)</td>
<td>28.3 (23.7–NE)</td>
<td>20.9 (18.4–23.8)</td>
<td>0.74 (0.57–0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>No RAS mutation, BRAF mutation</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months of progression-free survival — median (95% CI)</td>
<td>6.1 (3.7–10.7)</td>
<td>5.4 (3.3–6.2)</td>
<td>0.58 (0.29–1.15)</td>
<td>0.12</td>
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<tr>
<td>Months of overall survival — median (95% CI)</td>
<td>10.5 (6.4–18.9)</td>
<td>9.2 (8.0–15.7)</td>
<td>0.90 (0.46–1.76)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>RAS or BRAF mutation</strong></td>
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<td></td>
<td></td>
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<tr>
<td>No. of patients</td>
<td>296</td>
<td>305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months of progression-free survival — median (95% CI)</td>
<td>7.3 (6.3–7.7)</td>
<td>8.0 (7.5–9.0)</td>
<td>1.24 (1.02–1.49)</td>
<td>0.03</td>
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<tr>
<td>Months of overall survival — median (95% CI)</td>
<td>15.3 (12.7–17.6)</td>
<td>18.0 (15.9–20.8)</td>
<td>1.21 (0.99–1.47)</td>
<td>0.06</td>
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<tr>
<td><strong>No KRAS mutation in exon 2, other RAS or BRAF mutation</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of patients</td>
<td>75</td>
<td>86</td>
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<tr>
<td>Months of progression-free survival — median (95% CI)</td>
<td>6.7 (5.3–8.2)</td>
<td>7.3 (5.7–8.0)</td>
<td>1.05 (0.73–1.52)</td>
<td>0.80</td>
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<tr>
<td>Months of overall survival — median (95% CI)</td>
<td>14.5 (10.4–18.5)</td>
<td>15.8 (11.9–18.8)</td>
<td>1.14 (0.78–1.66)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Other potential biomarkers

KRAS testing
- Response rate: 24.4%
- Mutation rate: 41.2%
- Mutation rate in KRAS wild-type: 7.2%

BRAF testing
- Response rate: 36.3%

NRAS testing
- Response rate: 38.4%
- Mutation rate in NRAS wild-type: 4.8%

PIK3CA testing
- Response rate: 39.9%
- Mutation rate in PIK3CA: 3.1%

Quadruple wild-type: 50.3%

De Roock et al, Lancet Oncol 2010
RAS testing

- Tumour tissue
- Sent to external lab
- Extract DNA
- *KRAS, NRAS & BRAF*
- Funded by CDF
Biomarker summary

- Need to be KRAS and NRAS wild type to potentially benefit from anti-EGFR antibody
- RAS mutations are predictive not prognostic
- BRAF mutation – rare but signify poor prognosis
- No biomarker for anti-angiogenic agents
BUT.....

- This may all change as NICE currently evaluating anti-EGFR antibodies 1\textsuperscript{st} line
First line

Is there a RAS mutation?

- **NO**
  - Folfox +/- panitumumab
  - 12 weeks of chemo then CT, can have 6 week break then continue until PD

- **YES**
  - Are the platelets high or is there a high burden of visceral disease?
    - **YES**
      - Consider continuous chemo
        - FOLFOX/XELOX
        - 12 weeks of chemo then CT, can have 6 week break then continue until PD
    - **NO**
      - Intermittent chemo
        - FOLFIRI
        - FOLFOX/XELOX
        - 16-18 weeks of chemo then CT
        - Consider FOCUS 4 trial
Important eligibility:
Platelets <400
>6 months from adjuvant chemo
How do we choose?

- CDF/NICE guidelines
- RAS status
- Platelet count
- Burden of disease
- Performance status
- Patient choice
- Toxicity profile of drug
  - Existing neuropathy
  - Hair loss
  - XELOX anecdotally more toxic than FOLFOX
Continuous vs. intermittent

• Usually given with an antibody
• Prolonged PFS
• More s/e
• Patient choice
• High platelets—better with continuous
Liver directed therapies

• Surgery
• Radiofrequency ablation (RFA)
• Selective internal radiotherapy (SIRT)
• Stereotactic Ablative Body Radiotherapy (SABR)
RFA

During radiofrequency ablation, the surgeon deploys electrodes from a probe that deliver radiofrequency energy. This high heat causes death of tumor cells.

percutaneous surgical
SIRT

Eligibility

- Clinical progression during or following standard chemotherapy
- No clinical trial of SIRT available as alternative treatment
- WHO performance status of 0–2
- Life expectancy > 3 months
- Adequate LFTs/FBC
- Limited extra-hepatic disease
- No brain mets
### SIRT

**Fused PET/CT Imaging**

**CT Imaging**

**CA19-9**

85.2 U/mL

49.2 U/mL

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>ORR</th>
<th>SD</th>
<th>Median Survival Post-SIRT</th>
<th>Median Survival Post-Diagnosis</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment of progressive disease or chemo-refractory disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saxena¹</td>
<td>25</td>
<td>SIR-Spheres microspheres</td>
<td>24%</td>
<td>48%</td>
<td>9.3 months</td>
<td>20.4 months</td>
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<tr>
<td>Coldwell²</td>
<td>23</td>
<td>SIR-Spheres microspheres</td>
<td>45%</td>
<td>nr</td>
<td>74% alive at 14 months</td>
<td>nr</td>
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<tr>
<td>Khanna³</td>
<td>9</td>
<td>SIR-Spheres microspheres</td>
<td>66%</td>
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<td>13.5 months</td>
<td>20.0 months</td>
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<td>Rafi⁴</td>
<td>19</td>
<td>SIR-Spheres microspheres</td>
<td>79%</td>
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<td>11.3 months</td>
<td>24.7 months</td>
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<tr>
<td>Hoffmann⁵</td>
<td>33</td>
<td>SIR-Spheres microspheres</td>
<td>36.4%</td>
<td>51.5%</td>
<td>22 months</td>
<td>43.7 months</td>
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<tr>
<td>Gaba⁶</td>
<td>1</td>
<td>SIR-Spheres microspheres</td>
<td>1 CR</td>
<td></td>
<td>alive at 17 months</td>
<td>nr</td>
</tr>
</tbody>
</table>

**Key:** ORR: objective response rate (complete response + partial response) by RECIST; SD: stable disease; † retrospective study; nr: not reported; CR: complete response; na: not applicable
SABR

**Stereotactic Ablative Radiotherapy**
High dose radiotherapy – up to 3 times the dose of standard

- Delivered in 3 to 8 fractions (rather than 20-33)
- Highly accurate target positioning
- Verification of target positioning
- Focal (ablative) RT doses delivered
The future

- Personalised medicine
- Biomarker panels at presentation
Questions?