Oesophageal and pancreatic cancer case studies - Q&A with Panel

Presented by Dr Ian Chau with
Mr Satvinder Mudan
Dr Samir Zar
Dr Angela Riddell
Ms Ramani Sitamvaram

Case history 1

- 73 years old male
- Jan 12 presented with epigastric pain and weight loss of 5 pounds
- OGD showed ulcer in lesser curve between 42 and 46cm
- Biopsy showed moderately differentiated intestinal type adenocarcinoma HER2 negative
- Previously fit and healthy Still coaching for the London Irish Rugby Club
- PS=1

Staging CT T3N1
What further staging investigations would you recommend?

1) Endoscopic ultrasound
2) PET scan
3) Laparoscopy
4) Others

Case history 1 (cont’d)

- CT → T3N1 gastric antral tumour
  - Feb 12 PET/CT → T3N0M0

- Feb 12 Laparoscopy → tumour starting at level of OGJ involving cardia and extending along lesser curvature to the incisura
- Plan: (extended total gastrectomy)
What treatment would you recommend?

1) Surgery alone
2) Surgery followed by adjuvant chemotherapy
3) Surgery followed by adjuvant chemoradiation
4) Peri-operative chemotherapy
5) Neoadjuvant chemotherapy followed by surgery
6) Neoadjuvant chemoradiation followed by surgery
7) Others

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Multimodality treatment in operable gastric cancer

- Surgery
  - Post-operative chemotherapy
- Pre-operative chemotherapy
  - Surgery
    - Post-operative chemoradiation
      - Post-operative chemotherapy
Neoadjuvant and peri-operative chemotherapy in OGJ and gastric cancer

- UK MAGIC trial
- FNLCC 94012 – FFCD 9703 trial
- EORTC 40954 trial

MRC MAGIC Study

<table>
<thead>
<tr>
<th></th>
<th>CSC</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year survival (%)</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>5-year survival (%)</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>24</td>
<td>20</td>
</tr>
</tbody>
</table>

Benefit to CSC arm: 9

HR = 0.66, 95% CI: 0.53–0.81, p=0.0001

FNLCC ACCORD 07-FFCD 9703 trial

<table>
<thead>
<tr>
<th></th>
<th>n=113</th>
<th>n=111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable adenocarcinomas of the lower third oesophagus, OGJ (64%) or stomach.</td>
<td></td>
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</tr>
<tr>
<td>FP x2/3</td>
<td>5-year OS: 24% vs 36%</td>
<td></td>
</tr>
<tr>
<td>4-6 weeks</td>
<td>5-year DFS: 19% vs 34%</td>
<td></td>
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<tr>
<td>Resection</td>
<td></td>
<td></td>
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<tr>
<td>4-6 weeks</td>
<td></td>
<td></td>
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<tr>
<td>FP x3/4 or no treatment</td>
<td></td>
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<tr>
<td>DDP 100 mg/m² d1</td>
<td></td>
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</tr>
</tbody>
</table>

Case history 1 (cont’d)

- CT → T3N1 gastric antral tumour
- Feb 12 PET/CT → T3N0M0
- Feb 12 Laparoscopy → tumour starting at level of OGJ involving cardia and extending along lesser curvature to the incisura
- Plan: (extended total gastrectomy)
- Feb-Apr 2012 Enrolled into STO3 study
- Randomised to peri-operative ECX
- 14 Jun 2012 Laparoscopic total gastrectomy

ST03 (MAGIC-B) trial design

- Primary endpoint: overall survival
- Target recruitment: 1,100 patients (80% power to detect 10% increase in 5-year survival from 40% to 50%)

Revised STO 3 trial design

- HER 2 negative
- Type 2 and 3 OGJ and gastric adenocarcinoma
- HER 2 positive

- To detect 10% increase in 5-yr survival from 40% to 50%; 80% power; 2-sided α = 0.05
- To detect HR of 0.68 with 5-yr survival of control at 30%; 80% power; 2-sided α = 0.05

ECX x 3 Surgery ECX x 3

ECX x 3 Surgery + Bevacizumab Bev q3 weeks x6

ECX x 3 Surgery + Bevacizumab + Bevacizumab

ECX x 3 Surgery + Bevacizumab + Lapatinib x18 weeks
Case history 2

- 58 years old female
- May 11 presented with dysphagia and backache
- OGD showed ulcerated tumour at 22cm
- Biopsy showed invasive carcinoma which in part is clearly squamous with a component of poorly differentiated adenocarcinoma - thus considered to be adenosquamous carcinoma
- PMH: hypertension, hypercholesterolaemia
- Smoked 20-30 cigarettes per day for 30 years
- Height = 162cm Weight = 51.8kg
- PS=1

What further staging investigations would you recommend?

1) Endoscopic ultrasound
2) PET scan
3) MRI scan
4) Others
Case history 2 (cont’d)

- CT → T3N0 mid-oesophageal tumour
- EUS → T3N1
- Jun 11 PET/CT → T3N0M0

What treatment would you recommend?

1) Surgery alone
2) Surgery followed by adjuvant chemotherapy
3) Surgery followed by adjuvant chemoradiation
4) Definitive chemoradiation alone
5) Neoadjuvant chemotherapy followed by definitive chemoradiation
6) Peri-operative chemotherapy
7) Neoadjuvant chemotherapy followed by surgery
8) Neoadjuvant chemoradiation followed by surgery
9) Others
The Royal Marsden
Case history 2 (cont’d)
- CT → T3N0 mid-oesophageal tumour
- EUS → T3N1
- Jun 11 PET/CT → T3N0M
- Jun 11 enrolled into the SCOPE trial

UK NCRI SCOPE trial design

- Histologically confirmed T1-4 N0-1 carcinoma of the oesophagus (adenocarcinoma or squamous cell or undifferentiated carcinoma) or Siewert Type 1 OGJ tumour or Type 2 with no more than 2 cm mucosal extension into the stomach
- Not suitable for surgery either for medical reasons or through patient choice
- Primary endpoint: Overall survival
- To detect an improvement in 2 year OS from 35% to 47.5% (Hazard Ratio [HR] = 0.71) with 80% power at a 5% significance level a total of 420 patients (269 events) are required

Case history 2 (cont’d)
- CT → T3N0 mid-oesophageal tumour
- EUS → T3N1
- Jun 11 PET/CT → T3N0M
- Jun 11 enrolled into the SCOPE trial
- Randomised to neoadjuvant cisplatin/capecitabine followed by chemoradiation
- Jul-Sep 11 received neoadjuvant chemotherapy × 2 cycles followed by CRT
- Weight ↓ to only 44kg
When would you assess response after chemoradiation?

1) Immediately following completion of chemoradiation
2) 1 month after completion of chemoradiation
3) 3 months after completion of chemoradiation
4) 6 months after completion of chemoradiation

Case history 2 (cont’d)

- Dec 11 → CT showed favourable response
- Repeat EUS → ulcerated mucosa, no clear tumour
- Biopsy → no evidence of residual carcinoma
- May 12 repeat OGD and biopsy → no evidence of malignancy
- Oct 12 to Jan 13 further weight loss
- Jan 13 disease relapse in primary tumour
- Performance status too poor for further active anti-cancer treatment

Case 3

- Referred from Cyprus, 60yr old man
- Upper Abdominal discomfort for several months
- CT had shown dilated pancreatic duct in distal pancreas-IPMN
- Distal pancreatectomy and splenectomy, 2009
- Positive margin
Case 3
- Repeated attacks of pancreatitis

April, 2012

Case 3, Pseudocyst and phlegmon
Case 4
- Male 64 yrs
- Left renal colic, October 2011
- CT mass in distal pancreas
- Ca19.9-23, CEA 7

Case 4, Tail of pancreas with spleen and colon invasion, October 2011

Single liver metastasis, Oct 2011
Case 4
- Inoperable
- Locally advanced, vascular invasion, invasion into splenic hilum, transverse colon
- Single liver metastasis in segment 6/9 border
- Performance status
  - Very good

Systemic chemotherapy in advanced pancreatic cancer:

<table>
<thead>
<tr>
<th></th>
<th>Clinical Benefit</th>
<th>ORR</th>
<th>1-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>23.8%</td>
<td>5.4%</td>
<td>18%</td>
</tr>
<tr>
<td>(n=63)</td>
<td>4.8%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>5FU</td>
<td>p=0.002</td>
<td>p=NS</td>
<td>p=0.002</td>
</tr>
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</table>

Burris et al J Clin Oncol 1997
### Phase III trials of gemcitabine ± cytotoxic drugs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms</th>
<th>n</th>
<th>Overall survival p</th>
<th>Median</th>
<th>1-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heinemann et al Gem/Cisplatin</td>
<td>Gemcitabine</td>
<td>95</td>
<td>7.5 months</td>
<td>25.3%</td>
<td>0.15</td>
</tr>
<tr>
<td>(2006)</td>
<td>Gem/Cisplatin</td>
<td>95</td>
<td>6.0 months</td>
<td>24.7%</td>
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<td>Louvet et al Gem/Oxaliplatin</td>
<td>Gemcitabine</td>
<td>157</td>
<td>9.0 months</td>
<td>35%</td>
<td>0.13</td>
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<tr>
<td>(2005)</td>
<td>Gemcitabine</td>
<td>156</td>
<td>7.1 months</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Rocha Lima et al Gem/Irinotecan</td>
<td>Gemcitabine</td>
<td>173</td>
<td>6.3 months</td>
<td>20%</td>
<td>0.789</td>
</tr>
<tr>
<td>(2004)</td>
<td>Gemcitabine</td>
<td>169</td>
<td>6.6 months</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Abou-Alfa et al Gem/Exatecan</td>
<td>Gemcitabine</td>
<td>175</td>
<td>6.7 months</td>
<td>23%</td>
<td>0.52</td>
</tr>
<tr>
<td>(2006)</td>
<td>Gemcitabine</td>
<td>174</td>
<td>6.2 months</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Oettle et al Gem/Pemetrexed</td>
<td>Gemcitabine</td>
<td>283</td>
<td>6.2 months</td>
<td>21%</td>
<td>0.848</td>
</tr>
<tr>
<td>(2005)</td>
<td>Gemcitabine</td>
<td>282</td>
<td>6.3 months</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

### Phase III trials of gemcitabine ± platinum compounds

<table>
<thead>
<tr>
<th>Trial</th>
<th>Rx arms</th>
<th>n</th>
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<tr>
<td>(2005)</td>
<td>GEMOX</td>
<td>157</td>
<td>27%</td>
<td>9.0 months</td>
<td>35%</td>
<td>0.13</td>
</tr>
<tr>
<td>Heinemann et al GEM</td>
<td>GEM</td>
<td>256</td>
<td>14%</td>
<td>6.7 months</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>(2007)</td>
<td>GEM + PLAT</td>
<td>255</td>
<td>22%</td>
<td>8.3 months</td>
<td>NR</td>
<td>0.031</td>
</tr>
<tr>
<td>Poplin et al GEM (30 min)</td>
<td>GEM</td>
<td>275</td>
<td>6%</td>
<td>4.9 months</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>(2009)</td>
<td>GEM (FDR)</td>
<td>277</td>
<td>10%</td>
<td>6.2 months</td>
<td>22%</td>
<td>0.04</td>
</tr>
<tr>
<td>E6201</td>
<td>GEMOX</td>
<td>272</td>
<td>9%</td>
<td>5.7 months</td>
<td>21%</td>
<td>0.22</td>
</tr>
</tbody>
</table>

### ACCORD 11/ PRODIGE 4 trial design

- **GEMCITABINE**
  - 1000mg/m² weekly × 7 followed by 1 week’s rest and then weekly × 3 q4 weeks for 6 cycles

- **FOLFIRINOX**
  - Oxaliplatin 85mg/m² & leucovorin 400mg/m²
  - Irinotecan 180mg/m²
  - 5-FU 400mg/m² bolus then 2400mg/m² over 46 hours q2 weeks for 6 months

- **Primary endpoint:** overall survival

- **Target recruitment:** 360 patients (80% power to detect an increase in median survival from 7 to 10 months; HR=0.70; 2-sided α = 0.05)

*Conroy et al N Engl J Med 2011*
ACCORD 11/PRODIGE 4: Survival

Overall survival

Comparison of FOLFIRINOX versus GEM:
- FOLFIRINOX Median S(t) = 11.1 months
- GEM Median S(t) = 6.8 months

Progression free survival

Comparison of FOLFIRINOX versus GEM:
- FOLFIRINOX Median PFS(t) = 6.4 months
- GEM Median PFS(t) = 3.3 months


Case 4, Tail of pancreas with vascular invasion,
January 2012
Case 4
- 9 cycles of FOLFIRINOX
- Proceeded to operation
  - Disal pancreatectomy, splenectomy, transverse colon
  - No lesion visible on intraoperative ultrasound in liver

Case 4
- Liver resection based on pre-chemotherapy scans
- Histopathology: Tumour necrosis
Case 5

- 52 years old male
- Oct 2012 Presented with 2 months' history of epigastric discomfort, significant weight loss of 3 stones
- Sep 2012 OGD → polypoid mass
- Biopsies → chronic gastritis
- PS = 1
- CT → 8.5 x 6.3 cm large necrotic mass over distal pancreas connected to spleen and colon with separate peritoneal deposits
- Serum CA19-9 = 75,020
- US guided biopsy of peritoneal nodule → moderately differentiated highly desmoplastic metastatic adenocarcinoma consistent with pancreatic primary

Started on chemotherapy with FOLFIRINOX
Case 5

- Cycle 1 day 2 severe lethargy, retching and nausea
- Day 4 persistent vomiting, dehydration → admitted into RMH for iv hydration
- Over the next 2 days, developed large bowel obstruction

- Emergency laparotomy, small bowel resection, omental resection of metastasis and formation of end ileostomy
- Slow but steady post-operative recovery
- Weight ↓ from 55kg to 43kg in six weeks

Dec 2012 commenced on GEMCAP chemotherapy
NCRI GEM-CAP trial in advanced pancreatic cancer

Cunningham et al. J Clin Oncol 2009

Forest plot of meta-analysis of published randomized controlled trials (including current trial)

Cunningham et al. J Clin Oncol 2009

MPACT Study Design

Planned N = 841

1:1, stratified by KPS, region, liver metastasis

Primary endpoint:

- OS

Secondary endpoints:

- PFS and ORR by independent review (RECIST)
- Safety and tolerability by NCI CTCAE v3.0

Von Hoff et al. ASCO 2013
Overall Survival

PFS by Independent Review

Exome sequencing of pancreatic cancer
Exome sequencing of pancreatic cancer


Same fate as the patients
### Phase III trials of gemcitabine ± targeted therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms</th>
<th>n</th>
<th>Overall survival</th>
<th>Median 1-year</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bramhall et al (2002)</td>
<td>Gem/Marimastat</td>
<td>120</td>
<td>5.52 months</td>
<td>18%</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Gem/placebo</td>
<td>119</td>
<td>5.47 months</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Van Cutsem et al (2004)</td>
<td>Gem/Tipifarnib</td>
<td>341</td>
<td>6.4 months</td>
<td>27%</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Gem/placebo</td>
<td>347</td>
<td>6.07 months</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Moore et al (2007)</td>
<td>Gem/Erlotinib</td>
<td>285</td>
<td>6.24 months</td>
<td>23%</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Gem/placebo</td>
<td>284</td>
<td>5.91 months</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>


### NCIC GEM-Erlotinib trial

- **GEMCITABINE**
  - 1000mg/m² weekly ×7 q8 weeks, thereafter weekly ×3 q4 weeks
- **Placebo**
- **GEM-erlotinib**
  - Gemcitabine 1000mg/m² weekly ×7 q8 weeks, thereafter weekly ×3 q4 weeks
  - Erlotinib 100/150mg po od

n=284

Moore et al J Clin Oncol 2007

### NCIC Gem-erlotinib overall survival

![Graph showing survival probability over time](image)
## Phase III trials of gemcitabine ± targeted therapy

<table>
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<tr>
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<th>n</th>
<th>mPFS (months)</th>
<th>mOS (months)</th>
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<tbody>
<tr>
<td>Kindler et al (2010)</td>
<td>Gem/Erlotinib 301</td>
<td>301</td>
<td>3.6</td>
<td>6.0</td>
</tr>
</tbody>
</table>

|                          | Gem/placebo                  | 300| 2.9           | 5.9          |
|                          | Gem/placebo                  | 275| 3.7           | 7.8          |

| Van Cutsem et al (2009)     | p=0.0002                     |    | p=0.2087      |
| Kindler et al (2010)        | p=0.075                      |    | p=0.95        |
| Rougier et al (2013)        | p=0.8645                     |    | p=0.2034      |


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<td>372</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>Gem/placebo</td>
<td>371</td>
<td>3.0</td>
<td>5.9</td>
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<tr>
<th>Kindler et al Lancet Oncol 2011; Philip et al J Clin Oncol 2010</th>
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