Current state and future perspectives of neoadjuvant treatment of gastrointestinal carcinomas

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Disclosures

- **Travel and accommodation**: Lilly, Ipsen, Sanofi

- **Advisory Board**: Bayer, Lilly, Merck
Neoadjuvant setting

• Localised resectable disease

• All treatments given before surgery

• Surgery is the curative modality!
What can be achieved with neoadjuvant treatment?

1. Improve overall survival
2. Symptoms’ relief
3. Test of the tumor biology
4. Downstaging of the tumor
5. Allows surgical team to get ready
Current indications to neoadjuvant treatment

- Oesophagus cancer
- Gastric cancer
- Pancreatic cancer
- Rectal cancer
- Colon cancer
- Hepatocarcinoma
Oesophagus cancer
CROSS trial

Primary outcome: Overall Survival

ADK or SCC
OE or GOJ
T1N1 or T2-3
N0-1

R

Chemoradiotherapy then surgery

Weekly Carboplatine AUC2 and Paclitaxel 50mg/m² + RxT 41.5Gy over 5 weeks

Surgery upfront

N : 368

Von Haggen et al, NEJM 2012
Shapiro et al; Lancet 2015
CROSS trial

Von Haggen et al, NEJM 2012
Shapiro et al; Lancet 2015
# CROSS trial

<table>
<thead>
<tr>
<th></th>
<th>CRT &gt; S</th>
<th>S</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had surgery</td>
<td>94%</td>
<td>99%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Median time from randomisation to surgery</td>
<td>97 days</td>
<td>24 days</td>
<td></td>
</tr>
<tr>
<td>Unresectable during surgery</td>
<td>4%</td>
<td>13%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>In hospital mortality</td>
<td>4%</td>
<td>4%</td>
<td>NS</td>
</tr>
<tr>
<td>R0</td>
<td>92%</td>
<td>69%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ypT0N0</td>
<td></td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>pCR (ADK)</td>
<td></td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>pCR (SCC)</td>
<td></td>
<td>49%</td>
<td></td>
</tr>
</tbody>
</table>

Von Haggen *et al*, NEJM 2012

Shapiro *et al*; Lancet 2015
Futur directions in neoadjuvant treatment in oesophagus cancer

• Do pCR patients need to be operated?
  • PRODIGE 32 trial

• Role and impact of adding immunotherapy to CRT
  • ≈ 6 trials
Gastric cancer

Operable stage T1NO

- Consider endoscopic/limited resection

Operable stage >T1 NO

Preferred pathway

- Preoperative chemotherapy

- Surgery

Surgery

- Adjuvant chemoradiotherapy

- Adjuvant chemotherapy

Postoperative chemotherapy
Impact of peri-operative treatments in gastric cancer

FFCD
- Low OE / GOJ (75%)
- Gastric (25%)
- N : 224

RF
- Perioperative chemotherapy → surgery
  - Cisplatin 100mg/m² + 5FU 800mg/m² (D5) every 28D
- Surgery upfront

MAGIC
- Low OE / GOJ (25%)
- Gastric (75%)
- N : 503

RF
- Perioperative chemotherapy → surgery
  - Epirubicine 50mg/m², cisplatin 60mg/m², 5FU 200mg/m² D21
- Surgery upfront

Primary outcome: Overall Survival

Cunningham et al, NEJM 2006
Ychou et al; JCO 2011
Impact of peri-operative treatments in gastric cancer

FFCD

Log-rank $P = 0.02$
Hazard ratio = 0.69
(95% CI, 0.50 to 0.95)

MAGIC

Perioperative chemotherapy
Surgery alone

$P = 0.009$

Cunningham et al, NEJM 2006
Ychou et al; JCO 2011
Impact of peri-operative treatments in gastric cancer

FLOT 4

GOJ (55%)
Gastric (45%)

N : 716

Primary outcome: Overall Survival

Perioperative chemotherapy → surgery
Epirubicin 50mg/m², cisplatin 60mg/m², 5FU 200mg/m² D21

Perioperative chemotherapy → surgery
Docetaxel 50mg/m² + Oxaliplatin 85mg/m² + 5FU 2600mg/m² D1) every 15D

Cunningham et al, NEJM 2006
Ychou et al; JCO 2011
Al-Batran et al, Lancet 2019
Impact of peri-operative treatments in gastric cancer

Cunningham et al, NEJM 2006
Ychou et al; JCO 2011
Al-Batran et al, Lancet 2019
Impact of peri-operative treatments in gastric cancer

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<thead>
<tr>
<th></th>
<th>MAGIC</th>
<th>FFCD</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery performed</td>
<td>91.6%</td>
<td>96.5%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>96.4%</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td>TTS</td>
<td>99 days</td>
<td>78 days</td>
<td>79 days</td>
</tr>
<tr>
<td></td>
<td>14 days</td>
<td>13 days</td>
<td>92 days</td>
</tr>
<tr>
<td>R0</td>
<td>84%</td>
<td>74%</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>78%</td>
<td>85%</td>
<td>78%</td>
</tr>
<tr>
<td>Post-op mortality</td>
<td>5.6%</td>
<td>4.6%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>5.9%</td>
<td>4.5%</td>
<td>3%</td>
</tr>
<tr>
<td>Post op chemotherapy</td>
<td>49.5%</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52%</td>
</tr>
</tbody>
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If only 50% get adjuvant treatment, do we need adjuvant treatment?

Cunningham et al, NEJM 2006
Ychou et al; JCO 2011
Al-Batran et al, Lancet 2019
Impact of the MSI status

1. Chemotherapy and surgery, MSS or MSI-L
2. Chemotherapy and surgery, MSI-H
3. Surgery, MSS or MSI-L
4. Surgery, MSI-H

Smyth et al, Jama oncol 2017
Futur directions

INNOVATION study

Her-2 amp

Neoadjuvant immunotherapy +/- chemotherapy

TCGA, Nature, 2014
Biomarker driven trials

TOGA trial

Gastric cancer
Inoperable, recurrent, metastatic
PS 0–2
HER2 : 3+ (IHC) ou FISH+

5-FU or capecitabine + cisplatine (n=290)

5-FU or capecitabine + cisplatine + trastuzumab (n=294)

Turn around time > 2 weeks select good biology tumors

Bang et al., Lancet 2010
Hepatocellular Carcinoma

HCC in cirrhotic liver

Prognostic stage

Very early stage (0)
- Single <2 cm
- Preserved liver function
- PS 0

Early stage (A)
- Single or 2-3 nodules <3 cm
- Preserved liver function
- PS 0

Solitary

Optimal surgical candidate

Yes

No

2-3 nodules ≤3 cm

Transplant candidate

Yes

No

Treatment
- Ablation
- Resection
- Transplant
- Ablation

Survival
> 5 years

EASL Guidelines, 2018
HCC → R → Surgery

Surgery

Radiotherapy → Surgery

N: 164

Wei et al, JCO, 2019
pancreatic cancer patients

10-20% → resectable

30-40% → locally advanced/unresectable

50-60% → metastatic

Gillen et al, PLOS one, 2010
FOxTROT:
an international randomised controlled trial in 1052 patients evaluating neoadjuvant chemotherapy for colon cancer.

On behalf of the FOxTROT collaborative group
Colon cancer  
CT predicted T3-4, N0-2, M0  
Fit for surgery and chemo  
Not obstructed

2-year efficacy, ITT  
• recurrence or persistent disease

short-term efficacy  
• completeness of resection  
• stage and size of resected tumour  
• histological tumour regression grade

Surgery

6 wks NAC

18 wks AC

24 wks AC

Surgery

n=354

n=698
Primary outcome: 2-year efficacy

Recurrence – by treatment allocation

2-year recurrence, pre vs postop:
13.6% (95/698) vs 17.2% (61/354)
HR=0.75 (95%CI 0.55, 1.04), 2p=0.08

% with recurrence

Years from Randomisation

At risk:
post 354
preandpost 698
303 618
245 541
180 375
107 224
64 144

postop
pre & postop

27%
21%
## Completeness of resection

<table>
<thead>
<tr>
<th>Local pathologist score*</th>
<th>Neoadjuvant chemotherapy n=689</th>
<th>Straight to surgery n=353</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not proceed to surgery</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Surgery but no resection</td>
<td>0.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>R2 – macroscopically incomplete</td>
<td>0.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>R1 - microscopically incomplete</td>
<td>4.2%</td>
<td>8.8%</td>
</tr>
<tr>
<td>R0 - microscopically complete</td>
<td>93.1%</td>
<td>88.4%</td>
</tr>
</tbody>
</table>

*Concordance of local vs central assessment of resection margins = 99% (n=904)

P < 0.05
Key patient inclusion criteria

- Histologically confirmed colon cancer (no rectal cancer)
- No distant metastases
- No signs of perforation or clinical bowel obstruction

Futur directions

Colonoscopy + biopsies → dMMR (n=30) → MMR-P (n=30) → Ipilimumab 1 mg/kg D1 + nivolumab 3 mg/kg D1+15* → Surgery → Follow-up

7 dMMR → 5/7 CR, 7/7 → MR
7 pMMR → 0/7 CR

Primary outcome: Safety/feasibility
Rectal cancer

- Chemoradiotherapy
- Short course radiotherapy
- Following CRT or SCRT, 15 to 25% pCR

Maas et al, Lancet oncol, 2010
Total Neoadjuvant Therapy: TNT

Mix of chemotherapy and radio(chemo)therapy

No «standard» TNT

pCR estimation: 22.6%!!!
Is watchfull waiting for pCR a good idea?

C Disease-free survival for patients treated by surgery with cCR vs W&W

<table>
<thead>
<tr>
<th></th>
<th>W&amp;W</th>
<th>Surgery with cCR</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>3</td>
<td>10</td>
<td>65.6</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

Li et al (2015)⁴⁸
Total 5 48 13 118
Heterogeneity: τ²=0.00; χ²=0.13, DF=1 (p=0.71); I²=0%
Test for overall effect: Z=1.08, p=0.28

HR IV, random (95% CI)
0.65 (0.18-2.36)
0.43 (0.07-2.56)
0.56 (0.20-1.60)

D Overall survival for patients treated by surgery with cCR vs W&W

<table>
<thead>
<tr>
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<th>W&amp;W</th>
<th>Surgery with cCR</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>0</td>
<td>3</td>
<td>53.5</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

Li et al (2015)⁴⁸
Total 2 48 6 118
Heterogeneity: τ²=0.00; χ²=0.02, DF=1 (p=0.88); I²=0%
Test for overall effect: Z=1.39, p=0.16

HR IV, random (95% CI)
4.50 (0.33-62.28)
3.33 (0.20-55.69)
3.91 (0.57-26.72)

Dossa et al, Lancet Gastroenterol Hepatol, 2017
Futur directions

None surgical determination of pCR

- MRI, radioomics, ctDNA or combined approaches

Increase pCR frequency

- New drug combinations: IO + Radiotherapy or intensive chemotherapy
What is the future of neoadjuvant treatment in oncology?

Oncology drug approvals (FDA) by year
General perspectives in neoadjuvant treatment of gastrointestinal carcinomas

• A wave of immunotherapy + "something" is coming

• More and more biology driven neoadjuvant trials

  e.g: MSI-H in Gastric cancer
Thank you for your attention