Current standards and practice-changing studies in operable rectal cancer

June 10-11 2020

Rob Glynne-Jones
Mount Vernon Cancer Centre/
Champalimaud Foundation
DISCLOSURE SLIDE

I have no disclosures
In colon cancer, primary surgery followed by postoperative chemotherapy
2 LANDMARK PRACTICE CHANGING STUDIES IN LOCALLY ADVANCED RECTAL CANCER (LARC)
The Dutch TME trial

Primary endpoint: local control

N = 1805
Clinically resectable (stage I-III)

TME

SCRT → TME

- SCRT: 25 Gy in 5 fractions

Median follow-up 11.6 yrs

- 10-yr local relapse: 5% vs 11%, p<0.0001
- 10-yr distant relapse: 25% vs 28%, p=0.21
- 10-yr OS: 48% vs 49%, p=0.86

Pre- vs post-operative chemoradiation
CAO/ARO/AIO-94

Locoregional Recurrences

<table>
<thead>
<tr>
<th>Months</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>12</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>24</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>36</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>48</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>60</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

10 years overall survival 59.6% vs 59.9% (P =0.85).

There is a standard for chemoradiation

COLORECTAL CANCER – WHAT IS THE STANDARD OF CARE?

In colon cancer, primary surgery followed by postoperative chemotherapy

In rectal cancer, the standard of care has been preoperative short-course radiotherapy (5 x 5Gy) - SCPRT or long course chemoradiation (45- 50.4Gy) – LCCRT and then surgery

? +/- postoperative chemotherapy
HISTORICALLY IN CONTEXT OF 1990S

High local recurrence rates of 25-35%

Poor 5 year survival 40-50%
APER rates up to 60%
Perineal recurrence +++

Even with TME poor outcomes
If no RT

Oncologic outcomes following TME surgery alone*

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>10-year local recurrence</th>
<th>10-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3%</td>
<td>72%</td>
</tr>
<tr>
<td>II</td>
<td>8%</td>
<td>55%</td>
</tr>
<tr>
<td>III</td>
<td>19%</td>
<td>37%</td>
</tr>
</tbody>
</table>

* Data from the control group of the Dutch TME trial

* NB - No postoperative chemotherapy
Fig. 2. Radiotherapy (RT) for all patients diagnosed with rectal cancer in Sweden and Norway from 1996 to 2012.
SCPRT versus CRT: no significant difference in local control

Polish Trial (Bujko 2006)

14.4% vs 18.6%
P = 0.17

TROG-01 Trial (Ngan 2012)

7.5% vs 4.4%
P = 0.24
SCPRT versus CRT: Equivalence in overall survival

Polish trial (Bujko 2006)  Trans-Tasman trial (Ngan 2012)
Resectable Rectal AdenoCa

Primary endpoint: time to local recurrence
Pettersson et al  BJS 2010/ Erlandsson 2017
Stockholm III - Distant Metastases

- SRT vs SRT-delay p=0.362
- SRT vs LRT-delay p=0.738
- SRT-delay vs LRT-delay p=0.231

At risk:

<table>
<thead>
<tr>
<th></th>
<th>129</th>
<th>119</th>
<th>101</th>
<th>94</th>
<th>89</th>
<th>83</th>
<th>47</th>
<th>35</th>
<th>22</th>
<th>20</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT-delay</td>
<td>128</td>
<td>112</td>
<td>101</td>
<td>95</td>
<td>88</td>
<td>82</td>
<td>51</td>
<td>45</td>
<td>32</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>LRT-delay</td>
<td>128</td>
<td>116</td>
<td>98</td>
<td>90</td>
<td>87</td>
<td>84</td>
<td>52</td>
<td>39</td>
<td>31</td>
<td>27</td>
<td>15</td>
</tr>
</tbody>
</table>
SIMILAR ONCOLOGICAL OUTCOMES IN STOCKHOLM III

Cumulative incidence of local recurrence in the whole trial was no different:
- 8/357 (2.2%) patients who received SCPRT immediate surgery
- 10/355 (2.8%) who received SCPRT with delay

No increase in metastases with delay to SCPRT
Surgical morbidity better
SCPRT with a 25 Gy total dose at 5 Gy/fraction during 1 week, followed by immediate surgery (< 10 days from the first radiation fraction) [I, A];

SCPRT with delayed surgery is also a useful alternative to conventional short-course RT, with immediate surgery offering similar oncological outcomes and lower postoperative complications [57].
SO….IF IT IS ONCOLOGICALLY SAFE TO EXTEND THE INTERVAL……

Then ........you can fill with consolidation chemotherapy
Polish 2 Trial - fixed cT3/cT4 or locally recurrent rectal cancer without distant metastases

N = 541 patients

Primary endpoint: microscopically radical resection rate
Primary end-point [n=515]

R0 resection rates (surgery performed & pathologic R0 status):
- 77% for SCPRT with 3 cycles of chemotherapy
- 71% for CRT (control arm)
- (p=0.081)

Secondary end-points

<table>
<thead>
<tr>
<th></th>
<th>SCPRT + FOLFOX4</th>
<th>LCCRT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall acute toxicity</td>
<td>75%</td>
<td>83%</td>
<td>p = 0.006</td>
</tr>
<tr>
<td>Grade III/IV toxicities</td>
<td>23%</td>
<td>21%</td>
<td>NS</td>
</tr>
<tr>
<td>pCR rate</td>
<td>16%</td>
<td>12%</td>
<td>p = 0.17</td>
</tr>
</tbody>
</table>
Ciseł B, et al., Long-course preoperative chemoradiation vs. 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: Long-term results of the randomized Polish II study. Ann Oncol 2019
So 5 x 5 Gy followed by FOLFOX is an alternative to LCCRT alone
SINCE 1997 AND THE SWEDISH RECTAL CANCER TRIAL

Building on this standard SCPRT/LCCRT + TME + adjuvant chemo

No published trials successful in improving rate of metastases or overall survival (OS)
SINCE 1997 AND THE SWEDISH RECTAL CANCER TRIAL

Building on this standard SCPRT/LCCRT + TME + adjuvant chemo

No published trials successful in improving rate of metastases or overall survival (OS)
20-35% still develop metastases
SINCE 1997 AND THE SWEDISH RECTAL CANCER TRIAL

Building on this standard  SCPRT/LCCRT + TME + adjuvant chemo

No published trials successful in improving rate of metastases or overall survival (OS)
20-35% still develop metastases
Compliance to post-operative adjuvant chemotherapy is poor (mostly 43% [Chronicle]
- 58% [EORTC 22921])
SINCE 1997 AND THE SWEDISH RECTAL CANCER TRIAL

Building on this standard  SCPRT/LCCRT + TME + adjuvant chemo

No published trials successful in improving rate of metastases or overall survival (OS)
20-35% still develop metastases
Compliance to post-operative adjuvant chemotherapy is poor (mostly 43% [Chronicle] - 58% [EORTC 22921])
Compliance to neoadjuvant shown to be better in phase II trials (51%- 93%)

Fernandez-Martos 2010
HISTORICAL GOALS OF TREATMENT

Reduction in Local Recurrence Rate (almost 30%)

Preservation of anal sphincter (surgeon aspiration)

Increase in Disease free and Overall survival

(Preservation of quality of life and bowel/urinary and sexual function)
BUT INCREASINGLY

We want to extend overall survival

And we have increased response rates with combination chemotherapy……
Watch & Wait

Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy
Long-term Results

Angelita Habr-Gama, MD,* Rodrigo Oliva Perez, MD,* Wladimir Nodulin, MD,† Jorge Sabatás, MD,‡ Ulysses Ribeiro Jr, MD,‡ Afonso Henrique Silva e Sousa Jr, MD,* Fábio Guilherme Campos, MD,* Desidério Roberto Kiss, MD,* and Joaquim Gama-Rodrigues, MD‡

ARTICLE

Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer


Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

Maxime JM van der Valk, Denise E Hälling, Esther Bastiaanen, Elske Meershoek-Klein Kranenburg, Gerard J. Beets, Nuno I. Figueredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium*
And so now we have total neoadjuvant therapy (TNT)
The argument for Total Neoadjuvant Therapy (TNT)

.....“a pragmatic solution to the problems of delivering adjuvant chemotherapy postoperatively

- consistently
- within a reasonable time-frame (no delay)
- and administering appropriate and sufficient doses

- (a problem that has caused issues for randomised trials)
And so now we have total neoadjuvant therapy (TNT)

- designed to achieve both
SO DIFFERENT OPTIONS

Induction NACT  Chemo $\rightarrow$ SCPRT/LCCRT $\rightarrow$ TME

Consolidation NACT  SCPRT/LCCRT $\rightarrow$ Chemo $\rightarrow$ TME

NACT alone as alternative to RT
RAPIDO Trial NCT01558921.

920 patients

MRI based entry criteria

T4 EMVI + N2 CRM +

RANDOMIZATION

SCPRT 5X5 Gy

CapOx + 6

Capecitabine: 825 mg/m2
Oxaliplatin: 130 mg/m2

Standard CRT with capecitabine

22-24 weeks interval to surgery

8 weeks (±2 weeks)

Primary endpoint: Time to disease related Treatment Failure
Primary endpoint: Disease-free survival (DFS)
GAME CHANGERS FROM ASCO 2020

RAPIDO

3 year disease-related treatment failure (loco-regional failure, distant metastasis, a new primary colon tumor or treatment-related death)

23.7% in the experimental arm versus 30.4% in the standard arm (HR 0.76 [0.60 – 0.96]; \( p = 0.02 \)).

Probability of distant metastasis was also lower in the experimental arm - 19.8% vs 26.6% (HR 0.69 [0.53 – 0.89]; \( p = 0.004 \))
GAME CHANGERS FROM ASCO 2020

PRODIGE-23

3-yr DFS significantly improved in the NACT arm - **75.7% vs 68.5%** (HR 0.69, 95% CI 0.49-0.97, p=0.034).

3-yr MFS **71.7%** in the NACT arm vs **78.8%** (HR 0.64, CI 0.44-0.93, p<0.02) in standard LCCRT arm.
Polish 2 Trial - fixed cT3 /cT4 or locally recurrent rectal cancer without distant metastases

N = 541 patients

- SCPRT 5x5 GY
- FUFA weekly OXA CRT (50.4Gy in 28 fractions)

Primary endpoint: microscopically radical resection rate

The FOWARC trial – Design

Endpoints
Primary endpoint: 3 yr DFS

*Patients recruited from 15 Chinese Centres 2010-2015

Deng, J Clin Oncol 2016
NEOADJUVANT CHEMOTHERAPY WITH SYSTEMIC DOSES AND 3-4 MONTHS DURATION

Does reduce the risk of metastases!! (finally proof of principle)

Approximately 7% in both trials
Do you have to use FOLFOXIRI?
Is this for all?
Or can we select?
CURRENT STANDARDS

Staging/imaging
Surgery
Pathology

Essential components for delivering standard-of-care treatment
### Risk group | TN substage | Therapeutic options
--- | --- | ---
**Very early** | cT1 sm1 (-2?) N0 | Local excision (TEM). If poor prognostic signs (sm ≥ 2, high grade, V1), resection (TME) (or possibly CRT)

**Early (good)** | cT1-2; cT3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI | Surgery (TME) alone. If poor prognostic signs (crn+, N2) add postop CRT or CT⁺. (CRT with evaluation, if cCR, wait-and-see, organ preservation)

**Intermediate (bad)** | cT2 very low, cT3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited cT4aN0 | Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high risk patients for surgery)

**Advanced (ugly)** | cT3mrf+, cT4a,b, lateral node+ | Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT
Neoadjuvant Treatment: Options and Indications

CLINICAL PRACTICE GUIDELINES

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Glynne-Jones¹, L. Wynicz³, E. Tint³, E. Brown², C. Rödel², A. Cervantes⁷ & D. Arnold⁸, on behalf of the ESMO Guidelines Committee∗

Annals of Oncology 2017

Risk-Adjusted Treatment
RECTAL CANCER TREATMENT RECOMMENDATIONS

Very early disease cT1, sm1, N0
- Local RT may be used as an alternative to local surgery (+/- CRT)

Early disease cT1-ct2; cT3a/b if middle or high cN0 (cN1 if high), MRF clear, no EMVI
- TEM, CRT or 'watch-and-wait' for fragile, high-risk patients or those rejecting radical surgery
  - MRI to re-evaluate tumour

Intermediate disease cT3a/b very low, levators clear, MRF clear, cT3a/b in mid- or high rectum, cN1-2 (not extranodal), no EMVI
- TEM alone or SGPRT/CRT if good quality major rectal excision cannot be assured
  - MRI to re-evaluate tumour
  - 'Watch-and-wait' may be considered in high-risk patients if CR is achieved with CRT

Locally advanced disease cT3c/d or very low, levators not threatened, MRF clear cT3c/d mid-rectum, cN1-N2 (extranodal), EMVI+
- SCPRT or CRT
  - MRI to re-evaluate tumour
  - 'Watch-and-wait' may be considered in high-risk patients if CR is achieved with CRT

Advanced disease cT3 with any MRF involved, cT4b, levators threatened, lateral node+
- SCPRT plus FOLFOX and delay to surgery
  - MRI to re-evaluate tumour

TME (plus photographic record of specimen and assessment of TME quality)
- Further surgery if needed due to tumour overgrowth
- TME in most cases (plus photographic record of specimen and assessment of TME quality)
- TME in most cases (plus photographic record of specimen and assessment of TME quality)
ESMO GUIDELINES

We talk about EMVI, MRF and T3a/b ie T3 substage

For which MRI is essential
# Diagnostic Work-up in Primary Rectal Cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location (distance from anal verge)</td>
<td>DRE/Palpation&lt;br&gt; Rigid sigmoidoscopy (flexible endoscopy)*</td>
</tr>
<tr>
<td>Morphological verification</td>
<td>Biopsy</td>
</tr>
<tr>
<td>cT stage</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>ERUS&lt;br&gt; MRI&lt;br&gt; MRI (ERUS)*</td>
</tr>
<tr>
<td>Intermediate/advanced</td>
<td></td>
</tr>
<tr>
<td>Sphincter infiltration</td>
<td>MRI (ERUS, palpation, EUA)*</td>
</tr>
<tr>
<td>cN stage</td>
<td>MRI (CT, ERUS)*</td>
</tr>
<tr>
<td>M stage</td>
<td>CT, MRI (or US)* of the liver/abdomen&lt;br&gt; CT of the thorax&lt;br&gt; PET-CT if extensive EMVI for other sites</td>
</tr>
<tr>
<td>Evaluation for all patients</td>
<td></td>
</tr>
</tbody>
</table>

*Methods within brackets are less optimal

cN, clinical node stage; cT, clinical tumour stage; CT, computed tomography; DRE, digital rectal examination; EMVI, extramural vascular invasion; ERUS, endorectal ultrasound; EUA, examination under anaesthetic; MDT, multidisciplinary team; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; US, ultrasound

MDT Discussion
THE CURRENT STANDARD OF CARE MANAGEMENT OF LOCALIZED RECTAL CANCER:

You need

- High quality Magnetic Resonance Imaging (MRI) to provide accurate anatomical data
THE STANDARD OF CARE MANAGEMENT OF LOCALIZED RECTAL CANCER:

Initial MRI provides a roadmap for the surgeon

EMVI and threatened CRM

Demonstrates high risk factors
## SUBCLASSIFICATION OF T3 RECTAL CANCER

<table>
<thead>
<tr>
<th>DEPTH OF INVASION BEYOND THE MUSCULARIS PROPRIA in MM</th>
<th>MERCURY STUDY data</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3a &lt;1 mm</td>
<td>MRI and histopathology assessment of tumor spread are considered equivalent to within 0.5 mm (θR).</td>
</tr>
<tr>
<td>T3b 1-5mm</td>
<td></td>
</tr>
<tr>
<td>T3c 6-15mm</td>
<td></td>
</tr>
<tr>
<td>T3d &gt;15mm</td>
<td></td>
</tr>
</tbody>
</table>

Essential to interpret ESMO guidelines
## Clinical Lymph node staging

<table>
<thead>
<tr>
<th>Parameters of clinical lymph node staging in %.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer without neoadjuvant treatment</td>
</tr>
<tr>
<td>(n=21,629)</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>NPV</td>
</tr>
</tbody>
</table>

## Local Recurrence rates in CRO7 according the plane of surgery


<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Muscularis propria</th>
<th>Intra-mesorectal</th>
<th>Mesorectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>II</td>
<td>6%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>III</td>
<td>20%</td>
<td>14%</td>
<td>6%</td>
</tr>
</tbody>
</table>
### Local Recurrence rates in CRO7 according the plane of surgery


<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Muscularis propria</th>
<th>Intra-mesorectal</th>
<th>Mesorectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>II</td>
<td>6%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>III</td>
<td>20%</td>
<td>14%</td>
<td>6%</td>
</tr>
</tbody>
</table>
THE CURRENT STANDARD OF CARE MANAGEMENT OF LOCALIZED RECTAL CANCER:

Lymph nodes may only affect your local recurrence rate if you don’t do a full mesorectal excision and you leave them inside the patient.
THE CURRENT STANDARD OF CARE MANAGEMENT OF LOCALIZED RECTAL CANCER:

You need

- High quality Magnetic Resonance Imaging (MRI).
- Surgeons who perform high quality TME (with and without LCCRT)
THE CURRENT STANDARD OF CARE MANAGEMENT OF LOCALIZED RECTAL CANCER:
You need

- High quality Magnetic Resonance Imaging (MRI).
- Surgeons who perform high quality TME (with and without LCCRT)
- To know their local recurrence rate
THE CURRENT STANDARD OF CARE MANAGEMENT OF LOCALIZED RECTAL CANCER:

You need

- High quality Magnetic Resonance Imaging (MRI).
- Surgeons who perform high quality TME (with and without LCCRT)
- To know their local recurrence rate
- Pathologists to photograph/score the specimen
* May be difficult depending on resources available
THE CURRENT STANDARD OF CARE MANAGEMENT OF LOCALIZED RECTAL CANCER:

You need

- High quality Magnetic Resonance Imaging (MRI).
- Surgeons who perform high quality TME (with and without LCCRT)
- To know the local recurrence rate
- Pathologists who photograph and score the specimen and can confirm high quality – and feed back
- A functional MDT with a good chair
CONCLUSIONS - STANDARD OF CARE

MRI is essential component
If the CRM is threatened preoperative treatment is usually indicated
cEMVI+ is more important than cN+
SCPRT and LCCRT are acceptable alternatives for resectable cancer
SCPRT and consolidation chemotherapy is also acceptable
PRACTICE-CHANGING STUDIES
## Tumour response – PCR in the ‘timing’ trial

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (60) SG1</th>
<th>Cohort 2 (67) SG2</th>
<th>Cohort 3 (67) SG3</th>
<th>Cohort 4 (65) SG3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post CRT Chemo</td>
<td>none</td>
<td>2 cycles FOLFOX</td>
<td>4 cycles FOLFOX</td>
<td>6 cycles FOLFOX</td>
</tr>
<tr>
<td>Interval to surgery</td>
<td>8 weeks</td>
<td>11 weeks</td>
<td>15 weeks</td>
<td>19 weeks</td>
</tr>
<tr>
<td>pCR</td>
<td>11 (18%)</td>
<td>17 (25%)</td>
<td>20 (30%)</td>
<td>25 (38%)</td>
</tr>
<tr>
<td>pN0/N+</td>
<td>75%/25%</td>
<td>73%/27%</td>
<td>85%/15% (more T2)</td>
<td>79%/21%</td>
</tr>
</tbody>
</table>

NB RT dose was 54Gy

Garcia-Aguilar J Lancet Oncology 2015
The results of this phase II trial indicate that adding neoadjuvant mFOLFOX6 after CRT and increasing the time interval between CRT and surgery not only increases the rate of pCR response but also improves DFS
### DFS in the timing trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5 year DFS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>FOLFOX 2 CYCLES</td>
<td>81%</td>
<td>0.004</td>
</tr>
<tr>
<td>FOLFOX 4 CYCLES</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>FOLFOX 6 CYCLES</td>
<td>76%</td>
<td></td>
</tr>
</tbody>
</table>

The number of NACT cycles did not have dose-related effect on cancer-specific outcomes (Marco 2018) - in contrast to earlier where increasing NACT cycles led to an increased rate of pCR (Garcia Aguilar 2015).
## Polish 2 trial and RAPIDO trial compared

<table>
<thead>
<tr>
<th></th>
<th>Bujko 2016</th>
<th>Experimental arm 5 x 5 Gy + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post SCPRT Chemo</td>
<td></td>
<td>3 cycles FOLFOX</td>
</tr>
<tr>
<td>Interval to surgery</td>
<td></td>
<td>11 weeks</td>
</tr>
<tr>
<td>pCR</td>
<td></td>
<td>36/220 (16%) – ITT 13.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>RAPIDO Hospers 2020</th>
<th>Experimental arm 5 x 5 Gy + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post SCPRT Chemo</td>
<td></td>
<td>6 cycles CAPEOX</td>
</tr>
<tr>
<td>Interval to surgery</td>
<td></td>
<td>22-24 weeks</td>
</tr>
<tr>
<td>pCR</td>
<td></td>
<td>120/423 (28.3%) – ITT 26%</td>
</tr>
</tbody>
</table>

Bujko Ann Oncol 2016, Hospers ASCO 2020
## Compliance to trials of consolidation NACT

<table>
<thead>
<tr>
<th></th>
<th>No of patients in NACT arm</th>
<th>No of cycles of FOLFOX/ CAPEOX</th>
<th>% receiving Oxaliplatin</th>
<th>Dose reductions on Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPIDO</td>
<td>468</td>
<td>6 X XELOX</td>
<td>71% received 6 cycles of XELOX</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>84% received at least 75% of the prescribed courses</td>
<td></td>
</tr>
<tr>
<td>POLISH 2 (Bujko 2016, Cisel 2019)</td>
<td>261</td>
<td>3 X FOLFOX</td>
<td>70%</td>
<td>20%</td>
</tr>
</tbody>
</table>
## Induction with FoLFOX or CapeOx

<table>
<thead>
<tr>
<th></th>
<th>Induction pCR</th>
<th>Interval to surgery from end of CRT days</th>
<th>Standard CRT pCR</th>
<th>Interval to surgery from end of CRT days</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Marechal 2012</td>
<td>8/29 (28%)</td>
<td>Not given 6–8 weeks?</td>
<td>7/28 (25%)</td>
<td>Not given 6–8 weeks?</td>
<td>NS Abandoned for futility</td>
</tr>
<tr>
<td>Fernandez-Martos 2010, 2015</td>
<td>8/56 (14%)</td>
<td>Not given 5–6 weeks?</td>
<td>7/52 (14%)</td>
<td>Not given 5–6 weeks?</td>
<td>5 year DFS 64% vs 62% (NS)</td>
</tr>
</tbody>
</table>
MSKCC Randomised phase II Trial ‘OPRA’ NCT02008656

Stage II (T3-4, N-) or Stage III (any T, N+)

N = 325 patients

Primary endpoint 3 year DFS
CAO ARO AIO-12
NCT02363374

Primary endpoint pCR

cT3 < 6 - 12 cm with MRI > 5 mm (ie >cT3b), or resectable cT4 tumors, or clear cN+) on MRI

N = 311 patients
AIO-12 AND OPRA

Intensity of Oxaliplatin different
Duration of chemotherapy different
Dose of radiotherapy different (50.4Gy vs 54Gy)
Chemoradiation chemotherapy different (5FU/Oxaliplatin and capecitabine alone)
Interval from end of CRT to surgery different
(AIO-12 45 days vs 90 days – OPRA 8 vs 20 weeks?)
Conclusion: TNT Chemotherapy

- NACT feasible but some impact on LCCRT compliance if induction
- Proof of principle that NACT can impact on DFS and metastatic disease
- No evidence that TNT improves overall survival yet
- As yet unproven which is the best sequence induction or consolidation
- Selection may depend on aims of treatment
- More chemo / more chemo and longer interval offers higher response?
- No evidence in induction studies that TNT increases overall pCR
- Consolidation ? better for watch and wait than induction chemotherapy - but partly ? simply extending the interval to surgery
Thank you for listening