Future Prospects with Total Neo-Adjuvant Therapy in Rectal Cancer: The Optimal Sequencing of Multimodality Treatment in Rectal Cancer: The Medical Oncologist Point of View

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The Royal Marsden Hospital & Institute of Cancer Research
London and Surrey, UK
Disclosures

• Research funding: AstraZeneca, Celgene, MedImmune, Bayer, 4SC, Clovis, Eli Lilly, Janssen, Merck
Rectal tumours with high-risk MRI features require treatment before surgery

Adverse risk features:

1. T3b or above
2. Vascular deposits
3. Extramural venous invasion (EMVI)
4. Nodal involvement
5. Circumferential resection margin (CRM)
6. Low lying tumours

Rectal cancer

Early disease: cT1-cT2; cT3a/b if middle or high, cN0 (cN1 if high), CRM clear, no EMVI/vascular deposits

Surgery alone in most cases

Locally Advanced Rectal Cancer (LARC)

Neoadjuvant CRT prior to surgery

+/- adjuvant systemic chemotherapy
Baseline MRI with high-risk features

Extranodal vascular deposit with threatened CRM

Low lying tumour with EMVI
Neoadjuvant chemoradiotherapy is standard of care for T3-4 or N+ tumours

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Local recurrence (%)</th>
<th>5-yr DFS (%)</th>
<th>5-yr OS (%)</th>
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<tbody>
<tr>
<td>German CAO/ARO/AIO-94</td>
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<td>74</td>
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<td>9.7</td>
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<td><strong>p = 0.80</strong></td>
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<td><strong>p = 0.002</strong></td>
<td><strong>p = 0.52</strong></td>
<td><strong>p = 0.84</strong></td>
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2004 Neoadj CRT becomes standard of care

Sauer et al, NEJM 2004
Sauer et al, JCO 2012
Gerard et al, JCO 2006
Bosset et al, NEJM 2006
Addition of oxaliplatin to CRT does not improve clinical outcome

<table>
<thead>
<tr>
<th>Trials</th>
<th>Arms</th>
<th>n</th>
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<th>p</th>
<th>DFS (%)</th>
<th>OS (%)</th>
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*5-year survival rate

2004  Neoadj CRT becomes standard of care

2012  Capecitabine non-inferior to 5-FU in neoadjuvant CRT

2011-2018 Addition of oxaliplatin does not improve outcomes

Aschele et al, J Clin Oncol 2011
Gerard et al, J Clin Oncol 2012
Rodel et al, Lancet Oncol 2015
O’Connell et al, J Clin Oncol 2014
Allegra et al, J Natl Cancer Inst 2015
Schmoll et al, ASCO 2018
Distant relapse is still the main problem...

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<th>Study</th>
<th>n</th>
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Sauer et al, JCO 2012
Gerard et al, JCO 2006
Bosset et al, NEJM 2006
Is there a role for systemic chemotherapy in LARC...

- QUASAR study demonstrated increased benefit from adjuvant 5-FU based chemotherapy in higher risk colon and rectal cancer
- Only 6% of trial population (n=1622) received neoadjuvant radiotherapy

Quasar collaborative group, Lancet 2007
Is there a role for systemic chemotherapy in LARC following neoadjuvant CRT?

- Meta-analysis of individual patient data from four studies: i-CNR-RT, PROCTOR-SCRIPT, CHRONICLE and EORTC 22921 (n=1196)

- No improvement in distant relapse rate, DFS or OS with adjuvant 5-FU chemotherapy following neoadjuvant CRT

Breugom et al, Lancet Oncol 2015
... still no consensus

**ESMO guidelines**

“It is reasonable to consider adjuvant ChT in rectal cancer patients after preoperative CRT/RT with yp stage III (and ‘high-risk’ yp stage II)

The level of scientific evidence for sufficient benefit is much lower than in colon cancer and is probably limited to DFS rather than to OS.

The decision on postoperative CT (fluoropyrimidine alone or combined with oxaliplatin) should be risk-balanced, and made jointly by the individual and the clinician”

**NCCN guidelines**

“Adjuvant chemotherapy is recommended for all patients with stage II/III rectal cancer after neoadjuvant chemoRT and surgery if they did not receive neoadjuvant chemotherapy regardless of the surgical pathology results, although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well-defined.”

**NICE guidelines**

“Consider adjuvant chemotherapy for patients with high-risk stage II and all stage III rectal cancer to reduce the risk of local and systemic recurrence. [2011]”
What is the optimal sequencing of therapy in LARC?

Locally Advanced Rectal Cancer

Neoadjuvant CRT prior to surgery

+/- adjuvant systemic chemotherapy

?total-neoadjuvant therapy (TNT)
What are we trying to achieve with TNT?

- **To obviate the need for adjuvant chemotherapy?**
  - Improved tolerability of therapy to ensure effective delivery of treatment before surgery
  - Addressing drawbacks of poor adjuvant compliance
  - Treating micrometastases early

- **To obviate the need for surgery?**
  - Can we facilitate organ preservation?

- **To obviate the need for chemoradiotherapy?**
  - Can we avoid significant morbidity associated with pelvic radiotherapy?
Serial RMH phase II studies investigating TNT approach in MRI-defined higher risk LARC

- **Study**
  - Chemorad
  - EXPERT
  - EXPERT-C

- **Drugs**
  - 5-FU + Mitomycin C
  - CAPOX
  - CAPOX + Cetuximab

- **No of patients**
  - 36
  - 105
  - 164

- **Recruitment period**
  - Jan 99- Aug 01
  - Nov 01 – Aug 05
  - Aug 05 – July 08

**Notes:**
- MRI and CT scans at 12 weeks and after radiotherapy to reassess tumour response.
- 4-6 weeks rest for recovery of acute RT toxicity.
- Repeat MRI then TME SURGERY.
Administering neoadjuvant chemotherapy prior to CRT is feasible and safe

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>RR post chemo (%)</th>
<th>PD rate post chemo (%)</th>
<th>RR post CRT (%)</th>
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<tr>
<td>Chemorad</td>
<td>5-FU + Mitomycin C</td>
<td>27.8</td>
<td>0</td>
<td>80.6</td>
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<tr>
<td>EXPERT</td>
<td>CAPOX</td>
<td>74</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td>EXPERT-C</td>
<td>CAPOX + Cetuximab</td>
<td>64*</td>
<td>1*</td>
<td>84*</td>
</tr>
</tbody>
</table>

*All patients treated regardless of RAS status

Chau et al Brit J Cancer 2003
Chau et al J Clin Oncol 2006
Chua et al Lancet Oncol 2010
Dewdney et al J Clin Oncol 2012
Equivalent survival benefit achieved in higher risk LARC

EXPERT study (ITT n=105)

One or more MRI-defined high risk feature:

- CRM threatened/involved
- T3 low lying tumour
- Tumour extension ≥ 5mm into perirectal fat
- T4 tumours
- T1-4, N2

Median FU: 55 months

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<thead>
<tr>
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<th>3-year</th>
<th>5-year</th>
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</thead>
<tbody>
<tr>
<td>OS</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>PFS</td>
<td>68%</td>
<td>64%</td>
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Chua et al Lancet Oncol 2010
What are we trying to achieve with TNT?

• To obviate the need for adjuvant chemotherapy?
  • Improved tolerability of therapy to ensure effective delivery of treatment before surgery
  • Addressing drawbacks of poor adjuvant compliance
  • Treats micrometastases early

• To obviate the need for surgery?
  • Can we facilitate organ preservation?

• To obviate the need for chemoradiotherapy?
  • Can we avoid significant morbidity associated with pelvic radiotherapy?
TNT may increase clinical complete response (cCR) and facilitate organ preservation

Retrospective cohort analysis

Resectable LARC (T3/4 N+) N=811

Total neoadjuvant therapy (induction 5-FU and Oxaliplatin followed by CRT) N=410

CRT with adjuvant chemo N=320

pCR = 17%
cCR + W&W = 8%
Tumour regrowth = 9%

pCR = 18%
cCR + W&W = 24%
Tumour regrowth = 13%

Cercek et al JAMA Oncol 2018
What are we trying to achieve with TNT?

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- **To obviate the need for chemoradiotherapy?**
  - Can we avoid significant morbidity associated with pelvic radiotherapy?
Can we selectively eliminate neoadjuvant CRT in lower risk patients?

MSK pilot study, n=32

Study Outcome | No. | % | 95% CI
---|---|---|---
R0 resection rate | 32 | 100 | 89 to 100
Pathologic complete response rate | 8 | 25 | 11 to 43
Completion of neoadjuvant FOLFOX/bevacizumab | 30 | 93.8 | 79 to 99
Preoperative chemoradiation | 2 | 6.3 | 1 to 21
Postoperative radiation | 1 | 3.1 | 1 to 16
4-year local recurrence rate | 0 | 0 | 0 to 11
4-year disease-free survival | 27 | 84 | 67 to 94
4-year overall survival rate | 29 | 91 | 75 to 98

Abbreviation: FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin.
Can we selectively eliminate neoadjuvant CRT in lower risk patients?

Alliance Intergroup PROSPECT study

• Clinical stage T2 N1, T3 N0, or T3 N1 (stage IIA, IIIA or IIIB)
• Candidate for sphincter preservation TME before neoadjuvant therapy
• No encroachment on the mesorectal fascia based on preoperative imaging

NCT01515787
How to determine the optimal sequence of TNT for individual patients?

Circulating tumour DNA may guide systemic chemotherapy

Corcoran & Chabner N engl J med 2018
CtDNA during and post-CRT in LARC

Metastasis free survival by ctDNA detectability at each time-point

**Pre-treatment**
- Median of 6 days pre CRT
- % metastasis-free over time from consent (months)
- Subjects: 12, Events: 2 (17%), 35 (31%), 24 (69%)
- P = 0.33
- HR 2.1 (95% CI: 0.5-9.6)

**Mid CRT**
- Median of 21 days from start of CRT
- % metastasis-free over time from consent (months)
- Subjects: 37, Events: 10 (22%), 8 (60%), 5 (55%)
- P = 0.09
- HR 2.6 (95% CI: 0.9-8.1)

**End of CRT**
- Median of 37 days from end of CRT
- % metastasis-free over time from consent (months)
- Subjects: 37, Events: 10 (16%), 6 (77%), 3 (30%)
- P < 0.001
- HR 7.1 (95% CI: 2.4-21.5)

Royal Marsden Hospital Study: N=47

Khakoo et al. presented at the EACR-ESMO Joint conference on Liquid Biopsies 2019
CtDNA persistence during neo-adjuvant CRT can predict for the development of metastases

Metastasis Free Survival by ctDNA persistence compared to non-persistence

Pre-treatment & mid CRT ctDNA persistence

Pre-treatment, mid & end of CRT ctDNA persistence

Khakoo et al. presented at the EACR-ESMO Joint conference on Liquid Biopsies 2019
Detection of ctDNA following neoadjuvant CRT is associated with response determined by mrTRG

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-CRT ctDNA</th>
<th>P</th>
<th>Mid CRT ctDNA</th>
<th>P</th>
<th>End of CRT ctDNA</th>
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<td>N=35 n (%)</td>
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<td>MRI response by RECIST</td>
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<td>Good responders (CR and PR)</td>
<td>27 (77)</td>
<td>10 (83)</td>
<td>7 (70)</td>
<td>30 (81)</td>
<td>8 (80)</td>
<td>29 (78)</td>
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<td>Poor responders (SD and PD)</td>
<td>8 (23)</td>
<td>2 (17)</td>
<td>3 (30)</td>
<td>7 (19)</td>
<td>2 (20)</td>
<td>8 (22)</td>
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<td>MRI TRG response</td>
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<tr>
<td>Good responders (TRG 1-2)</td>
<td>14 (40)</td>
<td>6 (50)</td>
<td>3 (30)</td>
<td>17 (46)</td>
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<td>Poor responders (TRG 3-5)</td>
<td>21 (60)</td>
<td>6 (50)</td>
<td>7 (70)</td>
<td>20 (54)</td>
<td>9 (90)</td>
<td>18 (49)</td>
</tr>
</tbody>
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Khakoo et al 2019
Can we use ctDNA to determine which patients will benefit from TNT?

- ctDNA *during* neoadjuvant CRT can potentially identify patients more likely to develop distant relapse

- A significant proportion of these patients develop distant metastases *during or shortly after* completing neoadjuvant CRT

- These patients can be offered a more intensified neoadjuvant approach in a TNT setting

- Further investigation and validation of the use of ctDNA to guide treatment of LARC is warranted
Conclusions

• Neoadjuvant fluorouracil-based CRT is current standard approach for LARC
• Distant relapse is the main problem limiting survival
• Tailoring/sequencing of therapy may identify patients who can be spared morbidity from surgery or even pelvic radiotherapy
• Detection of risk factors and implementation of risk-adapted strategies are considered paramount in the management of rectal cancer for a personalised approach
Acknowledgements

Dr Avani Athauda and Dr Fiona Turkes

Clinical research fellows, GI and lymphoma unit, The Royal Marsden Hospital