Radiation Therapy in Locally Advanced Rectal Cancer

8th ESO, ESMO & Arab and Southern European Countries
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Outline

• Incidence & Facts

• RT in Locally advanced Rectal ca

• Future directions & Conclusion
Incidence

- Globally: 2\textsuperscript{nd} in F
- 3\textsuperscript{rd} in M
- 1.7 million new cases annually
- 2\textsuperscript{nd} cancer mortality (both sexes) after lung
- Lowest rates in Africa & South Central Asia
- Rising incidence < 50 years

Globocan 2018
Colorectal cancer
Source: Globocan 2018

Number of new cases in 2018, both sexes, all ages

- Lung: 2,093,876 (11.6%)
- Breast: 2,088,849 (11.6%)
- Prostate: 1,276,106 (7.1%)
- Stomach: 1,033,701 (5.7%)
- Cervix uteri: 569,847 (3.2%)
- Oesophagus: 572,034 (3.2%)
- Liver: 841,080 (4.7%)

Other cancers: 7,753,946 (42.9%)

Total: 18,078,957 cases

Number of deaths in 2018, both sexes, all ages

- Lung: 1,761,007 (18.4%)
- Breast: 880,792 (9.2%)
- Stomach: 782,685 (8.2%)
- Prostate: 508,585 (5.3%)
- Pancreas: 432,242 (4.5%)
- Liver: 781,631 (8.2%)
- Other cancers: 3,422,417 (35.8%)

Total: 9,555,027 deaths
Age standardized (World) incidence rates, colorectal cancer, males, all ages
<table>
<thead>
<tr>
<th>Country</th>
<th>Colorectal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Jordan</td>
<td>3</td>
</tr>
<tr>
<td>Cyprus</td>
<td>3</td>
</tr>
<tr>
<td>Egypt</td>
<td>8</td>
</tr>
<tr>
<td>France</td>
<td>3</td>
</tr>
<tr>
<td>Turkey</td>
<td>3</td>
</tr>
<tr>
<td>Lebanon</td>
<td>4</td>
</tr>
<tr>
<td>Iraq</td>
<td>4</td>
</tr>
<tr>
<td>Tunisia</td>
<td>3</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1</td>
</tr>
<tr>
<td>Morocco</td>
<td>3</td>
</tr>
<tr>
<td>Algeria</td>
<td>2</td>
</tr>
</tbody>
</table>
Are we making progress?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>54</td>
<td>68</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>Colon</td>
<td>52</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>82</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>69</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>Rectum</td>
<td>49</td>
<td>57</td>
<td>69</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>74</td>
<td>78</td>
<td>82</td>
</tr>
</tbody>
</table>

*5-year relative survival rates based on follow up of patients through 2006.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2006, Division of Cancer Control and Population Sciences, National Cancer Institute, 2009.
RT in Rectal Cancer - Facts
### Table 1. Definitions for T, N, M

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TX</strong></td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td><strong>T0</strong></td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td><strong>Tis</strong></td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>Tumor invades through the muscularis propria into the pericolorectal tissues</td>
</tr>
<tr>
<td><strong>T4a</strong></td>
<td>Tumor penetrates to the surface of the visceral peritoneum&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>T4b</strong></td>
<td>Tumor directly invades or is adherent to other organs or structures&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

#### Regional Lymph Nodes (N)

| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in 1-3 regional lymph nodes |
| N1a | Metastasis in one regional lymph node |
| N1b | Metastasis in 2-3 regional lymph nodes |
| N1c | Tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis |
| N2 | Metastasis in four or more regional lymph nodes |
| N2a | Metastasis in 4-6 regional lymph nodes |
| N2b | Metastasis in seven or more regional lymph nodes |

#### Distant Metastasis (M)

| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node) |
| M1b | Metastases in more than one organ/site or the peritoneum |

### Table 2. Anatomic Stage/Prognostic Groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Dukes&lt;sup&gt;*&lt;/sup&gt;</th>
<th>MAC&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3-T4a</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-T4a</td>
<td>N1-N1c</td>
<td>M0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4a</td>
<td>N2a</td>
<td>M0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

Note: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Patients who have a complete pathologic response are ypT0N0M0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.
Facts

- RT for rectal cancer was first introduced in the 1980s, in an attempt to decrease rates of local recurrence in patients with locally advanced rectal ca.

- One of the first RCTs to show decrease in local recurrence with the use of adjuvant therapy was published in 1985 by the Gastrointestinal Tumor Study Group (USA).

- First official recommendation for the use of adjuvant chemoradiation in patients with rectal ca came from the National Institutes of Health (NIH) consensus statement, published in 1990.
Although postoperative regimens were being optimized in 1990s within USA, around the same period investigators in Europe were exploring the potential benefits of treatment given in the preoperative setting (Neoadjuvant RT).

- Two different regimens of neoadjuvant RT were being assessed:
  - Long course RT, used mainly in USA
  - Short course RT, used mainly in Europe
Optimal Treatment

- Surgery alone
- Preop CT or CCRT
- Post Op Adj CT or CCRT
- CCRT
Local Recurrence Following Surgery alone:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Patients</th>
<th>Local Recurrence Rate</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC (Mobile)\textsuperscript{2}</td>
<td>235</td>
<td>34%</td>
<td>5 years (minimum)</td>
</tr>
<tr>
<td>NSABP R-01\textsuperscript{3}</td>
<td>184</td>
<td>25%</td>
<td>5.3 years (mean)</td>
</tr>
<tr>
<td>MRC (Fixed)\textsuperscript{5}</td>
<td>140</td>
<td>46%</td>
<td>5 years (minimum)</td>
</tr>
<tr>
<td>GITSG 7175\textsuperscript{7}</td>
<td>58</td>
<td>24%</td>
<td>6.7 years (median)</td>
</tr>
<tr>
<td>Norwegian (Tveit et al)\textsuperscript{15}</td>
<td>72</td>
<td>30%</td>
<td>4 years (minimum)</td>
</tr>
<tr>
<td>Stockholm II\textsuperscript{16}</td>
<td>285</td>
<td>27%</td>
<td>8.8 years (median)</td>
</tr>
<tr>
<td>Stockholm I\textsuperscript{17}</td>
<td>425</td>
<td>23%</td>
<td>4.4 years (median)</td>
</tr>
<tr>
<td>EORTC\textsuperscript{18}</td>
<td>228</td>
<td>31%</td>
<td>6.3 years (median)</td>
</tr>
<tr>
<td>Swedish Rectal Cancer Trial\textsuperscript{19}</td>
<td>585</td>
<td>27%</td>
<td>5 years (minimum)</td>
</tr>
</tbody>
</table>
Randomized Phase III Trials of Preoperative Radiotherapy Vs Surgery Alone as initial therapy for Resectable Rectal Cancer

5 yrs local control

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th></th>
<th>PREOPERATIVE RADIATION</th>
<th></th>
<th>Hazard Ratio</th>
<th>CI at 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Local Relapse Rate at 5 y</td>
<td>No.</td>
<td>Local Relapse Rate at 5 y</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWEDISH</td>
<td>585</td>
<td>27%</td>
<td>583</td>
<td>11%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>(1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUTCH</td>
<td>924</td>
<td>11.4%</td>
<td>937</td>
<td>5.8%</td>
<td>3.42</td>
<td>2.05-5.71</td>
</tr>
<tr>
<td>(2001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC CR07</td>
<td>676</td>
<td>17%</td>
<td>674</td>
<td>5%</td>
<td>2.47</td>
<td>1.61-3.79</td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>2185</td>
<td>17.3%</td>
<td>2194</td>
<td>6.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PREOPERATIVE RADIATION REDUCES SIGNIFICANTLY LOCAL RELAPSES EVEN IN TME RESECTED PATIENTS
Preoperative Radiation Alone

20 + Randomized Trials:

- Majority Short Course Hypofractionated RT
- All Decrease LR
- Swedish Rectal Cancer Trial Showed Survival Advantage; Problem = Ano-rectal Morbidity & Late Effects
Pre op CT/RT 10 yrs local control & OS (2600 patients)

T3/4 or N+

5-FU CRT + Surg vs ...

German Trial
n=823

Local Recurrences (10y)
pre CRT vs post CRT
7% vs 10% (p=.04)

Overall Survival (10y)
60% vs 60% (n.s.)

Sauer et al., J Clin Oncol 2012

French Trial
n=762

Local Recurrences (10y)
pre CRT vs pre RT
8% vs 16% (p<.05)

Overall Survival (10y)
68% vs 67% (n.s.)

Gerard et al., J Clin Oncol 2006

EORTC Trial
n=1011

Local Recurrences (10y)
pre CRT vs pre RT
12% vs 22% (p<.001)

Overall Survival (10y)
51% vs 49% (n.s.)

Bosset et al., Lancet Oncol 2014
Neoadjuvant Therapy: The German Study: A Shifting Concept

Design of the German Cancer Society's CAO/ARO/AIO-94 Randomized Trial

- Adenocarcinoma of the rectum
- Ultrasound T3, T4 or node positive
- Distal edge of tumor within 16 cm of anocutaneous line
- Deemed resectable by LA3 or APR with R0 resection likely
- No evidence of metastatic disease

**RANDOMIZE**

pT1-2 NO Patients
Observation

Arm 1
Surgery

**Within 4 Weeks of Surgery**

- Radiation: 1.8 Gy/day to 50.4 Gy to pelvis using 3 or 4 fields followed by a boost of 5.4 Gy in 1.8 Gy fractions to the tumor bed
- 5-FU: 1000 mg/m²/day continuous infusion for 120 hours on first and fifth week of radiation therapy
- 5-FU: 500 mg/m²/day bolus for 5 consecutive days every 4 weeks × 4 cycles

Arm 2

- Radiation: 1.8 Gy/day to pelvis using 3 or 4 fields
- 5-FU: 1000 mg/m²/day continuous infusion for 120 hours on first and fifth week of radiation therapy

**4-6 Weeks After Completion of Chemoradiation Surgery**

Cumulative incidence of local recurrence (%)

A

B

Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years


See accompanying editorial on page 1901; listen to the podcast by Dr Hong at www.jco.org/podcasts
Cumulative Incidence of Local Recurrences (%)  

- Preoperative treatment arm, 7.1%  
- Postoperative treatment arm, 10.1%  

$P = .048$

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop. CRT</td>
</tr>
<tr>
<td>0</td>
<td>393</td>
</tr>
<tr>
<td>30</td>
<td>327</td>
</tr>
<tr>
<td>60</td>
<td>280</td>
</tr>
<tr>
<td>90</td>
<td>251</td>
</tr>
<tr>
<td>120</td>
<td>166</td>
</tr>
<tr>
<td>150</td>
<td>68</td>
</tr>
<tr>
<td>180</td>
<td>6</td>
</tr>
</tbody>
</table>

|               | Postop. CRT |
| 0             | 396         |
| 30            | 341         |
| 60            | 296         |
| 90            | 263         |
| 120           | 170         |
| 150           | 67          |
| 180           | 6           |
Pre-Versus Postoperative CRT In Rectal Cancer: 11-Year Follow-Up

Fig 2. (A) Overall survival and (B) cumulative incidence of distant recurrences in the intention-to-treat population. CRT, chemoradiotherapy; preop, preoperative; postop, postoperative.
Sphincter Preservation

- Shrink the size or bulk of the tumor A to B make surgery easier (A to B)
- Shrink the location away from the sphincter making surgery possible (C to D)
- Avoiding permanent colostomy 39 - 94% (average 67%)
Sphincter preservation surgery in rectal cancer with neoadjuvant treatment

- 17 trials randomizing close to 10,800 pts.
- The rate of SSS has increased from:
  - as low as 14% in early 80s
  - 77% in 2008

Jean Prerre Gerard Crit. Rev. oncology/Hematology 2012
Total Mesorectal Excision TME

Figure 3: The definitions for defining quality of mesorectal excision [29].
(A) A complete mesorectal excision shows good bulk of mesorectum with a smooth surface and no defects. (B) A nearly complete mesorectal excision shows good bulk of mesorectum, but some defects or irregularities in the surface (arrowed) are present. (C) An incomplete mesorectal excision demonstrating a deep defect on the mesorectum below the peritoneal reflection, which allows visualisation of the muscularis propria (arrowed).
Indications of Neoadjuvant Therapy:

- T3 - T4 Lesions
- + LNs involvement
- T1 - 2 lesions with Positive Nodes
- Invasion of mesorectal fascia
- Low location tumors (sphincter preservation)

Br J Cancer 2000; 82:1131
Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Glynne-Jones¹, L. Wyrwicz², E. Tiret³, G. Brown⁵, C. Rödel⁶, A. Cervantes⁷ & D. Arnold⁸, on behalf of the ESMO Guidelines Committee

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†Approved by the ESMO Guidelines Committee: August 2002, last update May 2017. This publication supersedes the previously published version—Ann Oncol 2013; 24 (Suppl. 6): vi81–vi88.
### Table 6. Recommended choice of treatment options within TNM risk category of primary rectal cancer without distant metastases

<table>
<thead>
<tr>
<th>Risk group</th>
<th>TN substage</th>
<th>Possible therapeutic options</th>
<th>Further considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early</td>
<td>cT1 sm1 N0 (on ERUS and MRI)</td>
<td>Local excision (TEM) If pT1 and no adverse features, TEM is sufficient If adverse histopathology (sm ≥ 2, G3, V1, L1), requires radical resection (TME) as standard</td>
<td>Alternatively, in the case of adverse features on pathology, TEM plus salvage (or adjuvant) CRT in perioperative high-risk patients (but unproven benefit—with high risk of local recurrence for pT2)</td>
</tr>
<tr>
<td>Early (Good)</td>
<td>cT1 cT2; cT3a/b if middle or high, N0 (or also cN1 if high), MRF clear, no EMVI</td>
<td>Surgery (TME) alone is standard. If unexpected poor prognostic signs on histopathology (CRM+, extranodal/N2), consider postoperative CRT/CT (see postoperative recommendations in Table 7)</td>
<td>For fragile, high-risk patients or those refusing radical surgery (CRT with evaluation, local excision or if achieving cCR, ‘watch-and-wait’, organ preservation)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>cT3a/b very low, levators clear, MRF clear or cT3a/b in mid- or high rectum, cN1-2 (not extranodal), no EMVI</td>
<td>Surgery (TME) alone is a standard only if good-quality mesorectal resection assured (and local recurrence &lt;0.5% or, if not, preoperative SCPRT (5x5 Gy) or CRT followed by TME</td>
<td>If CRT is given and cCR is achieved, ‘watch-and-wait’ in high-risk patients for surgery may be considered</td>
</tr>
<tr>
<td>Bad</td>
<td>cT3c/d or very low localisation levators threatened, MRF clear cT3c/d mid-rectum, cN1–N2 (extranodal), EMVI+, limited cT4aN0</td>
<td>Preoperative SCPRT (5x5 Gy) or CRT followed by TME, depending on need for regression</td>
<td>If CRT and cCR achieved, ‘watch-and-wait’ in high-risk patients may be considered</td>
</tr>
<tr>
<td>Advanced (Ugly)</td>
<td>cT3 with any MRF involved, any cT4a/b, lateral node+</td>
<td>Preoperative CRT followed by surgery (TME and more extended surgery if needed due to tumour overgrowth), or preoperative SCPRT (5x5 Gy) plus FOLFOX and delay to surgery</td>
<td>Alternatively, 5x5 Gy alone with a delay to surgery in fragile/elderly or in patients with severe comorbidity who cannot tolerate CRT</td>
</tr>
</tbody>
</table>
Radiotherapy Techniques
CT simulation
(Belly Board)
GTV
Target Definition

CTV: Elective nodal regions

- **Standard**: Peri-rectal, internal iliac, and presacral (7 mm around vessels)
- For T4 tumors extending anteriorly: include external iliac
- For tumors invading anal canal: consider inguinal & external iliac
- **PTV**
  
  5-7 mm around CTV if perform daily IGRT; 1 cm if not
3D reconstruction of sites of relapse in patients with rectal cancer
CTV & PTV

CTV in mid-pelvis

CTVA covers:
- Rectum
- Mesorectum
- Internal iliac vessels
- Presacral space

Anterior margin: Extend 1 cm into posterior bladder wall

Moving superiorly in CTV

NOTICE: posterior border of CTV abuts external iliac vessels (which we do NOT include unless tumor invading prostate or seminal
anteriorly)

Lymph node

DO NOT include muscle or bone

Cephalad (superior) extent of CTV

Continue contour up to where the common iliacs bifurcate on L5/S1 interspace

Step 5: Add a margin for PTV

7-10mm margin on CTV is usually sufficient to account for pelvic motion

CTV+7mm = PTV

*Rad onc is amid a transition away from bony anatomy to guide contours (instead contouring soft tissue), but it still pervades in many ways – including pelvic nodal upper border (ie L5/S1)
3DCRT
Digitally Reconstructed Radiograph DRR
VMAT
Cone Beam CT scan (CBCT)
3DCRT Vs IMRT/VMAT
Acute Toxicity: 3D Vs. IMRT

Figure 1. Grade 2 or higher acute toxicity (%): 3D-CRT vs. IMRT

- Overall: $P=0.035$
- GI: $P=0.077$
- Diarrhea: $P=0.039$
- GU: $P=0.991$
- Heme: $P=0.160$
- Skin: $P=0.503$

**Dose**

- 45 – 50.4 Gy / 25-28 fractions or 25Gy/5 fractions
- 3DCRT, IMRT/VMAT
- IGRT (CBCT)
- Post Op 50.4 Gy / 28 fractions
- In-operable pts : 55Gy - 59.4 Gy /30 - 33 fractions
**NCCN Guidelines Version 1.2020**
**Rectal Cancer**

### NEOADJUVANT THERAPY

- Chemo/RT
  - Capcitabine + long-course RT\(^t\) or infusional 5-FU + long-course RT\(^t\)
  - (category 1 and preferred for both) or bolus 5-FU/leucovorin + long-course RT\(^p,r\)

- T3, N any with involved or threatened CRM (by MRI)\(^t\)
- T4, N any or locally unresectable or medically inoperable

- Chemotherapy (12–16 weeks)
  - FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine
  - Consider FOLFOXIRI (for T4, N+)

- Short-course RT\(^t\), followed by 12–16 weeks of chemotherapy
  - FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine

\(^t\) Restaging at 6 weeks post completion of RT

### PRIMARY TREATMENT

- Involved CRM or bulky residual disease
  - Consider FOLFOXIRI (for T4, N+)
  - Clear CRM

- Transabdominal resection\(^{1,w,y}\)
  - RT\(^p\)
  - or infusional 5-FU (preferred) + RT\(^p\) or bolus 5-FU/leucovorin + RT\(^p,r\)

### ADJUVANT TREATMENT\(^t\) (6 MO TOTAL PERIOPERATIVE TREATMENT PREFERRED)

- Chemo (12–16 weeks)
  - FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capcitabine
  - Consider FOLFOXIRI (for T4, N+)

- Transabdominal resection\(^{1,w,y}\)
  - Restaging\(^c\)
  - Resection contraindicated

- Systemic therapy\(^x\)
  - (See REC-F)

- Transabdominal resection\(^{1,w,y}\)
  - Restaging\(^c\)
  - Resection contraindicated

- Systemic therapy\(^x\)
  - (See REC-F)

- Observation (see REC-F)

\(^t\) See Principles of Imaging (REC-A).
\(^w\) See Principles of Surgery (REC-C).
\(^c\) CRM measured at the closest distance of the tumor to the mesorectal fascia. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphinceral plane.

\(^r\) Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capcitabine or

\(^y\) Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity. Short-course RT is not recommended for low-lying tumors, <6 cm from anal verge.

\(^y\) In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a “watch and wait,” nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams.

The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance.
Target Volumes
- Radiation therapy fields should include the tumor or tumor bed, with a 2- to 5-cm margin, the mesorectum, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields is encouraged.
- For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
- RT Dosing
  - 45-50 Gy in 25–28 fractions to the pelvis.
    - For resectable cancers, after 45 Gy a tumor bed boost with a 2-cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4–9.0 Gy in 3–5 fractions for postoperative radiation.
    - Small bowel dose should be limited to 45 Gy.
    - Short-course radiation therapy (25 Gy in 5 fractions) with surgery within 1 week of completion of therapy or delayed 6–8 weeks can also be considered for patients with stage T3 rectal cancer.
    - For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
    - If IORT is not available, 10–20 Gy external beam radiation therapy (EBRT) and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
Strategies for Optimizing Outcomes in Locally Advanced Disease

• Addition of oxaliplatin to standard chemoradiation

• TNT (total neoadjuvant therapy) protocol

• Selective Use of Radiation

• Watch & Wait
Impact of Oxaliplatin: NSABP R-04 Phase III Preoperative

Stratify

- T2 vs. T3
- M vs. F
- SP vs. APR

Capecitabine (825 mg BID) 50.4 Gy + Oxaliplatin (50 mg/m² qw)

CI 5-FU (225 mg/m²/d) 50.4 Gy ± Oxaliplatin (50 mg/m² qw)

n=1608
Primary Endpoint: LRR
*TME Not Mandated

Primary Endpoint: Local-Regional Control

5-FU vs. Cape

- 5-FU: 782 Pts, 95 L/R Recurrence
- Cape: 785 Pts, 97 L/R Recurrence
- HR = 1.00, 95% CI (0.75-1.32)
- P = 0.98

No Oxali vs. Oxali

- No Oxali: 641 Pts, 81 L/R Recurrence
- Oxali: 643 Pts, 76 L/R Recurrence
- HR = 0.94, 95% CI (0.67-1.29)
- P = 0.70

TNT (total neoadjuvant therapy) protocol
NRG-GI002 (TNT) Schema
Non-comparative Experimental Arms (PI George)
Current accrual = 174/174 as of 2/14/18

High Risk (distal, bulky, N2) Locally Advanced Rectal Cancer

FOLFOX x 8

FOLFOX x 8

FOLFOX + x 8

XRT + Capecitabine

XRT + Capecitabine + Veliparib

XRT + Capecitabine + Pembrolizumab

Surgery

Surgery

Surgery

Primary Endpoint: Reduction in NAR Score
NCT02921256

Coming soon

NRG-GI002 (TNT) Schema
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Primary Endpoint: Reduction in NAR Score
NCT02921256

Coming soon
Selective Use of Radiation
Who Needs Pelvic Radiation?
Intergroup Pooled Analysis of Postop Trials: T & N Stage

- 3791 Pts from 5 Phase III Trials (NCCTG, INT, NSABP R01 + R02): Outcome Analyzed by T & N Stage and Treatment:
  - **Intermediate Risk:** T1-2/N1 or T3N0
  - **Moderate Risk:** T1-2/N2, T3N1, T4N0
  - **High Risk:** T3N2, T4N1-2

PROSPECT N1048

(T2N1, T3N0/N1 5-12 cm) - PIs Shrag, Fichera (666/1060)

Hypothesis:
Treatment with neoadjuvant FOLFOX and selective use of preop 5FU-CRT for LARCs with curative intent sphincter sparing TME is not inferior to 5FU-CRT followed by surgery and FOLFOX
Organ Preservation ‘Watch & Wait’

- Organ preservation in patients with rectal ca is a highly appealing management approach

- It remains poorly understood how these results translate when attempted in a diverse practice setting; therefore not yet available for a prospective cooperative group trial

- Key is follow-up with rigorous imaging (pelvic MRI)
Select Organ Preservation Series
NOM (Non operative Management)

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Number of Centers Treating Patients</th>
<th>Total Radiation Dose</th>
<th>Rate of NOM</th>
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<tbody>
<tr>
<td>Habr-Gama et al.</td>
<td>2004</td>
<td>265</td>
<td>1</td>
<td>5040 cGy</td>
<td>26.8%</td>
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<tr>
<td>Habr-Gama et al.</td>
<td>2013</td>
<td>70</td>
<td>1</td>
<td>5400 cGy</td>
<td>50%</td>
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<tr>
<td>Maas M et al.</td>
<td>2011</td>
<td>21</td>
<td>1 (MSKCC)</td>
<td>5040 cGy</td>
<td>NR</td>
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<tr>
<td>Smith et al.</td>
<td>2012</td>
<td>32</td>
<td>1 (MSKCC)</td>
<td>5600 cGy</td>
<td>NR</td>
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<tr>
<td>Appelt et al.</td>
<td>2015</td>
<td>55</td>
<td>1</td>
<td>6000 cGy, IMRT + 5 Gy brachy boost</td>
<td>78%</td>
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</tbody>
</table>

Published:

<table>
<thead>
<tr>
<th>NCT</th>
<th>Status</th>
<th>Design</th>
<th>Total Radiation Dose</th>
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<tbody>
<tr>
<td>02008656</td>
<td>Accruing</td>
<td>Phase II</td>
<td>5040 cGy</td>
</tr>
</tbody>
</table>

Accruing:
On-going Watch & Wait Trial (NCT 02008656)

Stage II & III
n = 300

Randomize

CAPOX/FOLFOX x 6
50.4 Gy + 5FU/LV

50.4 Gy + 5FU/LV
CAPOX/FOLFOX x 6

50.4 Gy + 5FU/LV

No, Surgery

Yes, Watch & Wait

CCR
Short or Long Course RT ??
<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample Size</th>
<th>Local Recurrences @ 13 years</th>
<th>Local Recurrences @ 10 years</th>
<th>Overall Survival (13y)</th>
<th>Overall Survival (10y)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Trial</td>
<td>n=1168</td>
<td>9% vs 26% (p&lt;.001)</td>
<td>5% vs 11% (p&lt;.001)</td>
<td>38% vs 30% (p=.008)</td>
<td>48% vs 49% (n.s.)</td>
<td>Fokesson et al., J Clin Oncol 2005</td>
</tr>
<tr>
<td>Dutch Trial</td>
<td>n=1861</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>van Gijn et al., Lancet Oncol 2011</td>
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<tr>
<td>British Trial</td>
<td>n=1350</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sebag-Montefiore et al., Lancet 2009</td>
</tr>
</tbody>
</table>
Polish Trial

5x5 Gy  CRT

T1-3 Nany  5x5 Gy + immediate surgery

T3/4 or cN1-2  5-FU CRT + delayed surgery
<table>
<thead>
<tr>
<th>Polish Trial</th>
<th>5x5 Gy</th>
<th>CRT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Tox (Grade 3-4, %)</td>
<td>3</td>
<td>18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>pCR (%)</td>
<td>1</td>
<td>16</td>
<td>&lt;.001</td>
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<tr>
<td>CRM + (%)</td>
<td>13</td>
<td>4</td>
<td>0.02</td>
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<tr>
<td>Sphincter Preservation (%)</td>
<td>61</td>
<td>58</td>
<td>n.s.</td>
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<tr>
<td>Local Recurrences (4y, %)</td>
<td>11</td>
<td>16</td>
<td>n.s.</td>
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<tr>
<td>Overall Survival (4y, %)</td>
<td>67</td>
<td>66</td>
<td>n.s.</td>
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<tr>
<td>Late Tox (Grade 3-4, %)</td>
<td>10</td>
<td>7</td>
<td>n.s.</td>
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</table>

Med. F/U: 48 months

Bujko et al., Radiother Oncol 2004
Buiko et al., Br J Surg 2006
Pietrzak et al. Radiother Oncol 2007
<table>
<thead>
<tr>
<th>Trans-Tasman</th>
<th>5x5 Gy</th>
<th>CRT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Tox (Grade 3-4; %)</td>
<td>2</td>
<td>28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ypT0 (%)</td>
<td>1</td>
<td>15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sphincter Preservation (%)</td>
<td>63</td>
<td>69</td>
<td>0.22</td>
</tr>
<tr>
<td>Local Recurrences (3y, %)*</td>
<td>7.5</td>
<td>4.4</td>
<td>0.24</td>
</tr>
<tr>
<td>Overall Survival (5y, %)</td>
<td>74</td>
<td>70</td>
<td>0.62</td>
</tr>
<tr>
<td>Late Tox (Grade 3-4, %)</td>
<td>5.8</td>
<td>8.2</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Med. F/U: 5.9 years

*< 5 cm from AV: 6/48 vs 1/31 pts (p = 0.21)

Ngan SY et al., J Clin Oncol 2012
Palliating Pelvic Relapses

• Pain response rates in 64 – 85% range
• One series complete relief was:
  # bleeding (80-90%)
  # pain (65%)
  # mass (24%)
• Dose: 30Gy/10 or 37.5/15 frs
  (tumor with 1-2 cm margins)
Conclusion

- Standard of care for stage II/III disease is long course preoperative CRT (45-50 Gy RT & 5FU/cape), TME 6-10 weeks later and CTX (FOLFOX)

- Current ongoing and developing studies are:

  Upfront chemo, novel radiosensitizers and risk-based treatments (selective use of RT & watch & wait) in an attempt to optimize outcomes while minimizing morbidities

- Multidisciplinary approach
Thank you