Update on the Management of Locally Advanced Rectal Cancer

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Disclosures

- None
From a Historical Perspective

- Locally Advanced Rectal Cancer
  - **1981: 30% worldwide recurrence rate**
    - Anderson et al
    - Review of world literature
    - Local Recurrence for Restorative Proctectomy
      - 10-20% for Specialists
      - 40% for generalist
    - 80-90% evident by year 2

2. Heald, BJS 1982
From a Historical Perspective

“The mesorectum in rectal cancer surgery is the clue to pelvic recurrence”

Heald BJS 1982

I. Cawthorne Lancet 1990
From a Historical Perspective

- Prospective Study (n=80)
  - Looked at LRM (lateral resection margin) vs survival and recurrence
  - LRM >1mm or <1mm
  - Recurrence rates
    - >1mm= 17%
    - <1mm= 50%
  - **Significant survival benefit >1mm LRM**

Irene, Cancer 1993
“Specimen-Oriented” Surgery
Fig. 4 Actuarial analysis of local recurrence. Postoperative deaths within 30 days were excluded. -----, Group 1: ---, group 2. \( P = 0.03 \) (log rank test)

Fig. 5 Actuarial analysis of crude survival. Postoperative deaths were included. ----, Group 1: ---, group 2. \( P = 0.03 \) (log rank test)

Arbmann, BJS 1996
From a Historical Perspective (XRT+TME)

- Stockholm I & II
- Dutch Colorectal Cancer Group
- Prospective randomized trial
- XRT+TME (n=924)
  - 5 Gy × 5 days
- TME only (n=937)
  - recurrence rate @ 2yrs
    - XRT+TME=2.4%
    - TME only=8.2%

1. Martling, Lancet 2001
2. Kapitieijn, NEJM 2001
Fast Forward to the Present

- Routine Use of 5-FU/XRT with TME
- Local Recurrence 4-8%
- Survival of LARC versus Colon Ca
  - SEER Database (1995-2008)
    - 372,130 patients
    - Mean follow up 32 months

Lee, PLoS One 2013
Fast Forward to the Present

- Routine Use of 5-FU/XRT with TME
- Local Recurrence 4-8%
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  - SEER Database (1995-2008)
    - 372,130 patients
    - Mean follow up 32 months

Lee, PLoS One 2013
Contemporary Rectal Cancer Treatment

- Rectal Cancer has equivalent if not better survival than colon cancer stage for stage
- How do we respond to the constantly changing treatment modalities?
- Are these options for the better or worse?
- Do these options create too much variability in outcomes?
  - Which of these options are actually supported by literature?
Contemporary Rectal Cancer Treatment
LARC (T3/N or T1-2/N1-2)

- Neoadjuvant therapy
  - 5-FU/Cap + Long Course XRT
  - 5-FU/Cap + Short Course XRT
  - Short course XRT

- Total Neoadjuvant Therapy (TNT)
  - FOLFOX then 5-FU/Cap/LXRT then surgery
  - 5-FU/Cap/LXRT then FOLFOX then surgery
  - FOLFOX then 5-FU/Cap/SXRT then surgery
  - 5-FU/Cap/SXRT then FOLFOX then surgery
LARC (T3/N or T1-2/N1-2)

- Even more options…….
  - MRI guided therapy
    - MERCURY trial
  - Watch and wait for Complete Clinical Responders (CCR)
    - Watch and wait with Transanal Excision
Short Course Radiotherapy

- The most commonly used neoadjuvant regimen
  - 25-28 treatments over 5 weeks
  - 5000 rads
  - With infusional 5-FU or oral capecitabine

- Short course
  - 2500 rads over 5 days
  - Immediate surgery
    - 1-2 weeks
  - Delayed surgery
    - 6-8 weeks
Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

- 840 pts
  - 3-arm randomization
    - Short course and immediate surgery
    - Short course with delay
    - Traditional long course/chemo and surgery in 4-8 weeks
- Primary endpoint
  - Local recurrence

Erlandsson, Lancet 2017
No difference in local recurrence in any arm

Postop complications

- Greater in short course with immediate surgery than pts with short course and delay
Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

Johan Erlandsson, Torbjörn Holm, David Pettersson, Åke Berglund, Björn Cedermark, Calin Radu, Hemming Johansson, Mikael Machado, Fredrik Hjern, Olof Hallböök, Ingvar Syk, Bengt Glimelius, Anna Martling

Points to consider

- Bulky tumors?
- Threatened circumferential resection margin?
- APR rate in short course group is twice the rate in the traditional long course chemorads group
- Effective tumor downsizing?

Erlandsson, Lancet 2017
Short-course Versus Long-course Neoadjuvant Therapy for Non-metastatic Rectal Cancer: Patterns of Care and Outcomes From the National Cancer Database

- Pts between 2004-2014
  - 28,193 patients
    - Only 205 patients (0.7%) received short course radiotherapy

Dutta, Clin Col Ca 2018
No difference in overall survival

Long course radiation pt almost 3 times more likely to get pCR than short-course

- 17.9% versus 6.4% (p<.001)

Dutta, Clin Col Ca 2018
Total Neoadjuvant Therapy

- TNT for Locally Advanced Rectal Tumors
  - Why not give both the adjuvant and neoadjuvant therapy all before the rectal resection?
  - Could this make marginally resectable tumors or bulky tumors easier to resect for cure? Can we get more cCR or pCR results?
- Cap/OX or 5-FU/OX before or after RAD±5-FU then resect
- Multiple Phase II and III trials
  - EXPERT, EXPERT-C, STAR-01, PRODIGE-2, AVACROSS, etc
Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre phase 2 trial


Garcia-Aguilar, Lancet Oncol., 2015
Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial


<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=60)</th>
<th>Group 2 (n=67)</th>
<th>Group 3 (n=67)</th>
<th>Group 4 (n=65)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological complete response</td>
<td>11 (18%)</td>
<td>17 (25%)</td>
<td>20 (30%)</td>
<td>25 (38%)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Partial response</td>
<td>44 (73%)</td>
<td>50 (75%)</td>
<td>46 (69%)</td>
<td>39 (60%)</td>
<td>..</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (8%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>..</td>
</tr>
</tbody>
</table>

Data are number (%). p value tests the null hypothesis of equal proportions across study groups.

Table 3: Pathological tumour response

Primary endpoint: pCR

“the improvement in response is not associated with tumour progression, an increase in technical difficulty, or surgical complications”
MRI Assessment of CRM

- Close but clear
MRI Assessment of CRM

- Involved/Positive Margin
11 European Centers

- Rectal Cancers assessed via MRI
- Goal: Assessing whether or not MRI can predict a margin negativity/positivity

Fig 1 Recruitment of patients and treatment arms (MRI=magnetic resonance imaging)

354/408 had negative margins (87%, 95% CI 83-90%)

Specificity of clear margin by MRI 92% (327/354, 90-95%)

MRI predicted clear margin in 349 patients

- 327 had clear margins at time of surgery (94%, CI 94-96%)

One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer

F. G. M. Taylor¹, P. Quirke², R. J. Heald⁴, B. Moran⁴, L. Blomqvist⁶, I. Swift¹, S. St Rose⁵, D. J. Sebag-Montefiore³, P. Tekkis⁵ and G. Brown⁵, on behalf of the MERCURY study group
Magnetic Resonance Imaging–Detected Tumor Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience

- Subgroup analysis of MERCURY cohort
  - 111 patients
    - Rectal Cancer treated with neoadjuvant therapy
    - MRI with TNM staging and assessment of CRM
      - Assessed for response to neoadjuvant therapy
      - Tumor regression grade (TRG)
    - Determine associations with poor and good responders on MRI with survival outcomes

1. Patel, JCO 2011
Magnetic Resonance Imaging–Detected Tumor Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience

Fig 1. Trial progress flowchart. MRI, magnetic resonance imaging.
Magnetic Resonance Imaging–Detected Tumor Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience

Fig 2. Kaplan-Meier analysis of survival. (A) Post-treatment pathologic T stage (ypT) and overall survival; (B) ypT and disease-free survival; (C) tumor regression grade by magnetic resonance imaging (mTRG) and overall survival; and (D) mTRG and disease-free survival.

1. Patel, JCO 2011
MRI and “Optimized TME Surgery”

- Can MRI identify a subset of locally advanced rectal cancer patients who can go straight to surgery without neoadjuvant therapy?
Preoperative High-resolution Magnetic Resonance Imaging Can Identify Good Prognosis Stage I, II, and III Rectal Cancer Best Managed by Surgery Alone

*A Prospective, Multicenter, European Study*

- Can MRI identify “good prognosis” Stage I, II, III patients who can go straight to surgery *without* neoadjuvant therapy?
  - T2/3a/3b tumors with less than 5mm spread from the muscularis propria and safe CRM
  - 374 patients in Mercury trial
    - 122 (33%) defined as “good prognosis”
      - Overall survival at 5 years= 68%
      - Disease free survival at 5 years= 85%
      - Local recurrence rate= 3%

I. Taylor, Annals of Sur 2011
MERCURY Group

- Staging of rectal cancer via MRI is reproducible
- MRI can accurately identify and predict threatened circumferential margin
- MRI defined CRM is predictive of outcome
- MRI can qualitatively define tumor response to neoadjuvant therapy and is predictive of survival outcomes
- MRI can help identify a subset of rectal cancers that may not necessarily need neoadjuvant therapy and can go directly to surgery
MRI and “Specimen-Oriented Surgery”

- **MRI**
  - Some patients may need more than just traditional neoadjuvant therapy
    - Total Neoadjuvant Therapy versus clinical trials
  - Some patients may not need neoadjuvant therapy
  - Surgery and neoadjuvant therapy can be tailored to each patient’s particular tumor characteristics

- **MERCURY** data combined with the recently published Stockholm III have rapidly expanded therapeutic option for patients
  - Short course, short-course with delay and long course

1. Erlandsson, Lancet 2017
Non-Operative Management of LARC

“Watch and Wait” Approach

- Non-operative observation of clinical complete responders (cCR) after neoadjuvant radiotherapy
- Pioneered by Angelita Habr Gama
  - Results first published in 2004
    - 71 patients
- Until recently largest series was 129 patients
- 110 manuscripts
- 33 review articles
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

- 1009 patient registry
- 47 institutions
- 15 countries
- 880 patients included in manuscript
- Mean follow-up 3.3 years

van der Valk, Lancet 2018
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

Results

- Local regrowth occurred in 213 of 880 patients
  - 2-year rate of 25.2% (95% CI 22.2–28.5%)
  - 64% diagnosed in first year
  - 88% diagnosed by year two
  - Local regrowths were located in the bowel wall in 97% (206 of 213)
  - Only 3% of regrowths were to regional LN’s only and not in bowel wall

van der Valk, Lancet 2018
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

- Intervention for patients with recurrence
  - Information available on only 69% of patients (148 of 213)
  - Of the 148 recurrences
    - 115 underwent TME
      - 101 for curative intent
    - Remainder of patients underwent transanal excision

van der Valk, Lancet 2018
**Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWDD): an international multicentre registry study**

- **Critique**
  - Registry data
  - Entirely investigator driven
    - Unclear if they have data abstractors/auditors
  - Heterogeneous population
  - 25% recurrence higher than expected from other series
  - Unclear if all patients eligible are placed in database
  - Mode of follow up is variable
  - No data on 31% of the recurrences
  - **Paradigm shifts need to be based on cleaner data**

van der Valk, Lancet 2018
Surgical Technique and LARC

- Open Total Mesorectal Excision
- Laparoscopic Total Mesorectal Excision
- Robotic Low Anterior Resection
- Transanal Total Mesorectal Excision (taTME)
Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes
The ACOSOG Z6051 Randomized Clinical Trial

- Randomized multi-center trial
- Laparoscopic versus open LAR for curable LARC
  - 240 laparoscopic
  - 222 open
- Non-inferiority trial
  - Via composite outcome
    - Distal margin >1mm
    - Circumferential margin >1mm
    - Completeness/intactness of the mesorectal envelope
- **Result:** Unable to prove non-inferiority of laparoscopic versus open LAR

Fleshman, JAMA 2015
Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer
The ALaCaRT Randomized Clinical Trial

- Australasian Multicenter, Randomized Trial
- Laparoscopic versus open LAR for curable LARC
  - 238 laparoscopic
  - 237 open
- Non-inferiority trial
  - Via composite outcome
    - Distal margin >1mm
    - Circumferential margin >1mm
    - Completeness/intactness of the mesorectal envelope
- **Result:** Unable to prove non-inferiority of laparoscopic versus open LAR

Stevenson, JAMA 2015
Laparoscopic Versus Open Low Anterior Resection for Rectal Cancer: Results from the National Cancer Data Base

- National Cancer Database
  - 18,765 patients
  - Lap LAR 34.3%
  - Open LAR 65.7%
  - Propensity matched

- Small benefit to Laparoscopic over open LAR
  - Complete resection (91.6% vs 88.9, p<0.001)
  - Gross & microscopic margins(p<0.001)
  - Circumferential margin greater than 1mm (p<0.001)

Nussbaum, JGIS 2015
Minimally Invasive Versus Open Low Anterior Resection

Equivalent Survival in a National Analysis of 14,033 Patients With Rectal Cancer

- NCDB (2010-2012)
- 14,033 patients
  - 42.2% MIS LAR
  - 57.8% Open LAR
- Followed to 36 months
  - No difference in overall survival

Sun, Ann Surg 2016
Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer

Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial

- Interim follow-up
  - 462 eligible
  - Median follow-up: 47.9 mo
  - No difference in 2 year disease-free survival
  - No difference in local/regional recurrence

Fleshman, Ann Surg 2018
Disease-free Survival and Local Recurrence After Laparoscopic-assisted Resection or Open Resection for Rectal Cancer

The Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial

- ALaCaRT trial
- Interim analysis
- 475 patients
- Median follow-up: 3.2 years
  - No difference in 2-year recurrence, DFS or OS

Stevenson, Ann Surg 2018
What about Robotic LAR for Curable Rectal Cancers?
Robotic Low Anterior Resection for Rectal Cancer

A National Perspective on Short-term Oncologic Outcomes

- NCDB
- 6403 patients
- 956 Robotic LAR
  - No difference in short term outcomes and oncologic outcomes Robot vs Lap LAR and Open LAR
- Robotic LAR: lower conversion rate
  - 9.5% vs 16.4% (p<0.001)

FIGURE 1. Adjusted odds of short-term complications and oncologic outcomes for LLAR and RLAR, compared to the traditional open approach.

Speicher, Ann Surg 2015
Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer The ROLARRR Randomized Clinical Trial

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. With Outcome/Total No. (%)</th>
<th>Unadjusted Risk Difference (95% CI), %</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion to open</td>
<td>28/230 (12.2)</td>
<td>4.1 (-1.4 to 9.6)</td>
<td>0.61 (0.31-1.21)</td>
<td>.16</td>
</tr>
<tr>
<td>laparotomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRM+</td>
<td>14/224 (6.3)</td>
<td>1.1 (-3.1 to 5.4)</td>
<td>0.78 (0.35-1.76)</td>
<td>.56</td>
</tr>
</tbody>
</table>

Jayne, JAMA 2017
Transanal Total Mesorectal Excision (taTME)
Transanal Total Mesorectal Excision (taTME)

Figure 1. Transanal view. A: Rectal purse-string closure and tattoo marking. B: Full thickness circumferential transection.

Arroyave, EJSO 2017
Transanal Total Mesorectal Excision (taTME)

Figure 2. Down-to-up dissection. A: Anterior plane. B: Posterior plane.

Arroyave, EJSO 2017
Comparison of short-term clinical outcomes between transanal and laparoscopic total mesorectal excision for the treatment of mid and low rectal cancer: A meta-analysis

- 7 studies
  - 209 taTME
  - 257 Lap TME
- No difference in
  - Lymph node harvest
  - Distal margin
  - Hospital stay
  - Complications
  - Conversion
- Slightly favors taTME in the quality of the TME and CRM

Xu, EJSO 2016
taTME: A Few Questions….

- Learning curve
  - Prostatic or membranous urethral injury
- Function after intersphincteric proctectomy
  - Limited body of literature
    - Thought to be poor function
- Facilitated by two-team approach
- Equipment and space can be issue
Incidence and Risk Factors for Anastomotic Failure in 1594 Patients Treated by Transanal Total Mesorectal Excision

Results From the International TaTME Registry

Operative time, mean ± SD (range)

<table>
<thead>
<tr>
<th>Description</th>
<th>Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total operative time, hours:minutes</td>
<td>4:12 ± 1:42 (0:30–12:13)</td>
</tr>
<tr>
<td>Perineal phase time, hours:minutes</td>
<td>2:03 ± 1:03 (0:14–7:47)</td>
</tr>
</tbody>
</table>

Intraoperative adverse events

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical problems during transanal phase</td>
<td>330 (18.0)</td>
</tr>
<tr>
<td>Incorrect dissection plane</td>
<td>91 (5.7)</td>
</tr>
<tr>
<td>Pelvic bleeding &gt;100 mL</td>
<td>67 (4.2)</td>
</tr>
<tr>
<td>Visceral injuries during transanal phase, total</td>
<td>28 (1.8)</td>
</tr>
<tr>
<td>Urethral injury</td>
<td>12 (0.8)</td>
</tr>
<tr>
<td>Rectal tube perforation</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Vaginal perforation</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Hypogastric nerve divisions</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Bladder perforation</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

Percentages for missing values use the total number of cases as the denominator (ie, 1594). Percentages for the variables are calculated out of the total number of actual results available excluding the missing values.
COLOR III: a multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer

- Superiority trial
  - Primary endpoint: Circumferential resection margin
- Secondary endpoints
  - Intactness of mesorectum
  - Local recurrence
  - Overall survival
  - Disease free survival

Deijen, Surg Endosc 2018
Hospital Volume?  Hospital Type?

- What do we know?
Looking at Variation of Care

- Surgeon volume
- Variations within a single health system
  - Published abstract DDW 2018
  - “Surgeon-level Variation in Utilization of Local Staging and Neoadjuvant Therapy for Stage II-III Rectal Adenocarcinoma”
    - 9 Hospital System (Intermountain Healthcare, Utah)
    - 2010-2016
    - 240 patients
      - Local staging omitted in 43/240 (17.9%)
      - Neoadjuvant therapy omitted in 41/240 (17.1%)
        - Lack of NT associated with positive CRM, node positivity, and local recurrences (all p values significant)
        - Variation among surgeons

Swords, DDW 2018
High Rate of Positive Circumferential Resection Margins Following Rectal Cancer Surgery

OSTRiCH consortium
NCDB 2010-2011
16,619 patients with stage I-III rectal cancers
- patients with positive circumferential margin: 2859 (17.2%)
- Double the rate in European literature
- Why the disparity?
  - Use of neoadjuvant therapy
  - Surgical technique
  - High resolution MRI to identify threatened margin
  - Other

Rickles, Ann Surg 2015
Locally Advanced Rectal Cancer: Too Many Options?

T3N1 low rectal cancer

- Staging
- Neoadjuvant therapy
- Surgery
- Adjuvant therapy

> 240 unique permutations of care
Can we get the simple things right?

Evaluating the Current Status of Rectal Cancer Care in the US: Where We Stand at the Start of the Commission on Cancer’s National Accreditation Program for Rectal Cancer

Brady, JACS 2018
Evaluating the Current Status of Rectal Cancer Care in the US: Where We Stand at the Start of the Commission on Cancer’s National Accreditation Program for Rectal Cancer

- Joint effort CoC and ACS
- National Accreditation Program for Rectal Cancer
- NCDB (39,068 patients)
  - Looked at completion of staging, treatment started <60 days after diagnosis, CEA, tumor regression grading
  - NAPRC performance measures
    - Proximal/distal/circumferential margins, >12 lymph nodes

Brady, JACS 2018
Evaluating the Current Status of Rectal Cancer Care in the US: Where We Stand at the Start of the Commission on Cancer’s National Accreditation Program for Rectal Cancer

- Results
  - 85% of patients had clinical staging and treatments started within 60 days
  - Only 65% had pretreatment CEA
  - Only 28% had all the process measures completed
  - Only 56% of patients had all margins negative and greater than 12 LN’s on final pathology
  - Treatment at high volume centers (>30 cases per year) had higher odds of meeting all performance measures

Brady, JACS 2018
What next?

- Standardization of Care
  - TME in Europe only happens in centers of excellence
  - Regionalization of care in the US not possible and simply not fair to the patients
    - Financial toxicity of care
- Multi-disciplinary care a must
  - Surgeon is “captain of the ship”
  - Fit each therapeutic option to patient
    - Model of breast and pancreatic cancer
  - Outcomes must be audited regularly