Is there still room for improvement in surgery for locally advanced rectal cancer?

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39th ESMO congress 26 – 30 September 2014
Disclosure slide

• No disclosures
Is there still room for improvement in surgery for locally advanced rectal cancer?
Improvement in surgery for locally advanced rectal cancer

Options:

• Extended resection
• Improving functional outcome
• Robotic surgery
• NIR fluorescence imaging
• Auditing
• Organ preservation
5 major goals in treatment of a patient with rectal cancer

1. Local control
2. Long-term survival
3. Preservation of anal sphincter
4. Preservation of pelvic nerves, for GI, bladder and sexual function
5. Maintenance or improvement in QoL
High risk tumors

• Achieving a R0 resection
  – Required extent of the resection more challenging
  – ‘En bloc’ resection of the involved organs and structures
  – Very heterogeneous presentation
    • More different surgical solutions to achieve a radical en bloc resection
    • More differentiate or personalized approach required
    • Beyond TME Collaborative: high risk patients should be referred to a specialized center
The Swedish Rectal Cancer Trial (SRCT), TME trial, CAO/ARO/AIO-94 trial, EORTC 22921 trial and Polish Rectal Cancer Trial (PRCT) an APR procedure was associated with:

- increased risk of CRM involvement (OR 2.52, p < 0.001)
- increased LR rate (HR 1.53, p = 0.001)
- decreased CSS rate (HR 1.31, p = 0.002)

Den Dulk EJSO 2009
Risk factors for adverse outcome after abdominoperineal resection

- Age
- T stage
- N stage
- CRM
- Distance of the tumor to the anal verge
- Tumor location

### Unsatisfactory results APR

<table>
<thead>
<tr>
<th></th>
<th>CRM+</th>
<th>LAR</th>
<th>APR</th>
<th>P</th>
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<tbody>
<tr>
<td>More</td>
<td>CR+</td>
<td>10.7%</td>
<td>30.4%</td>
<td>0.002</td>
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</table>

More extensive surgical procedure needed?
Improvement in surgery for locally advanced rectal cancer

Options:

- Extended resection
- Improving functional outcome
- NIR fluorescence imaging
- Auditing
- Organ preservation
- Centralization to specialized centers
Inter-sphincteric APE
Short-term results extralevator abdominoperineal excision from Swedish Colorectal Cancer Registry

• Entire group: Extralevator APE did not result in fewer intraoperative perforations

• But fewer intraoperative perforations for:
  – Low tumours (≤4cm)
  – Early (T0-2) T-stages

• More postoperative wound complications for extralevator APE

Ischio-anal APE
Evidence of the Oncologic Superiority of Cylindrical Abdominoperineal Excision for Low Rectal Cancer

Nicholas P. West, Paul J. Finan, Claes Anderin, Johan Lindholm, Torbjorn Holm, and Philip Quirke

27 Cylindrical
101 Standard
Extended APR with gluteus maximus flap

- Mesorectum is not dissected off the levator muscles
- Perineal dissection is done in prone position
- *En bloc* resection levator muscles with the anus and lower rectum

Holm T *Br J Surg* 2007
Extended APR with gluteus maximus flap

Holm T Br J Surg 2007
Extended APR with gluteus maximus flap

<table>
<thead>
<tr>
<th></th>
<th>All procedures</th>
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<th>Curative procedures</th>
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<td>Extralevator APE (n = 176)</td>
<td>Standard APE (n = 124)</td>
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<td>Extralevator APE (n = 142)</td>
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<td>Time to discharge (days)*</td>
<td></td>
<td>14 (11–19)</td>
<td>15 (12–22)</td>
<td>0.054†</td>
<td>14 (11–19)</td>
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<td>Wound complications</td>
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<td>Yes</td>
<td></td>
<td>57 (38.0)</td>
<td>11 (20)</td>
<td>0.019†</td>
<td>50 (40.3)</td>
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<td>Infection/breakdown/sinus</td>
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<td>41 (72)</td>
<td>7 (64)</td>
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<td>5 (9)</td>
<td>1 (9)</td>
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<td>4 (8)</td>
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<td>Other</td>
<td></td>
<td>11 (19)</td>
<td>3 (27.3)</td>
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<td>No</td>
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<td>93 (62.0)</td>
<td>44 (80)</td>
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<td>74 (59.7)</td>
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<td>69</td>
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<td>18</td>
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<td>Sexual/urinary problems</td>
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<td>Yes</td>
<td></td>
<td>13 (30)</td>
<td>12 (24)</td>
<td>0.640†</td>
<td>11 (29)</td>
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<tr>
<td>Erectile dysfunction</td>
<td></td>
<td>6 (46)</td>
<td>4 (33)</td>
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<td>5 (45)</td>
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<tr>
<td>Urinary tract infection</td>
<td></td>
<td>0 (0)</td>
<td>3 (25)</td>
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<td>6 (46)</td>
<td>2 (17)</td>
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<td>5 (45)</td>
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<td>1 (8)</td>
<td>3 (25)</td>
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<td>1 (9)</td>
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<tr>
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<td></td>
<td>30 (70)</td>
<td>37 (76)</td>
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<td>27 (71)</td>
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<td>133</td>
<td>75</td>
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Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). APE, abdominoperineal excision. †Fisher’s exact test unless indicated otherwise; ‡Mann–Whitney U test.
Lateral nodes
Standard of care in Japan

Tumor is located at or below the peritoneal reflection

- Preoperative or intra-operative assessment for presence of LN metastases is not reliable.

Rb & T2 or more

Lateral node dissection
Stage II, III

low rectal cancer

n=700

Primary endpoint: Disease-free survival

JCOG0212

Japan Clinical Oncology Group

closed to accrual

Stage II, III

ME

ME+

Lateral lymph node dissection
Japanese trial – Lateral lymph node dissection

• Stage II – III rectal cancer

• TME alone versus TME + lateral lymph node dissection

• Lateral lymph node dissection:
  – Longer operation time (median 360 min vs. 254 min, p<0.0001)
  – More blood loss (576 ml vs. 337 ml, p<0.0001)
  – More grade 3-4 complications (22% vs. 16%, p=0.07)
## Comparison Dutch and Japanese results

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LR</th>
<th>n</th>
<th>%</th>
<th>% in N+</th>
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<tr>
<td>Japanese</td>
<td>324</td>
<td>6.9%</td>
<td>8</td>
<td>2.2</td>
<td>6.0</td>
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<tr>
<td>RT+TME</td>
<td>379</td>
<td>5.8%</td>
<td>3</td>
<td>0.8</td>
<td>2.1</td>
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<td>TME alone</td>
<td>376</td>
<td>12.2%</td>
<td>11</td>
<td>2.7</td>
<td>7.9</td>
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</table>

RT is as good as extended lymph node dissection.
Improvement in surgery for locally advanced rectal cancer

Options:

• Extended resection
• **Improving functional outcome**
• Robotic surgery
• NIR fluorescence imaging
• Auditing
• Organ preservation
History of rectal cancer surgery in Japan

1970  Extended surgery

1978  Komatubara initially reported NSS

1980

1984  Nerve Sparing Surgery

Based on better understanding of pelvic neuro-anatomy

Optimize function without compromising local control

2000
TME with autonomic nerve preservation

• Prospective study urogenital function
• Yoshihiro Moriya
• 50 Dutch patients

→ No urinary dysfunction

19 male patients complete nerve preservation: no sexual dysfunction
Autonomic nerve preservation

• Direct association between specific nerve damage and dysfunction
• Autonomic nerve preservation is achievable
• However, excellent results of experts have not been reproduced in large trials
Autonomic nerve preservation

‘We only see what we look for and we only look for what we know’

Walsh

Improvement in surgery for locally advanced rectal cancer

Options:

• Extended resection
• Improving functional outcome
• Robotic surgery
• NIR fluorescence imaging
• Auditing
• Organ preservation
Robotic Surgery

• Aims to eliminate many of the technical difficulties

• Rectal cancer: few studies.
  – Not established a benefit over standard laparoscopic surgery in terms of:
    • Technical, functional or oncological outcomes
Randomized trial – Robotic-assisted Tumor-specific mesorectal excision

- April 2006 – February 2007, \( n = 36 \)

- Robotic versus laparoscopic surgery for rectal cancer

→ No difference observed in operative times, conversion rates, or the quality of mesorectal excision

→ Length of hospital stay significantly shorter in robotic surgery

Robot-assisted Tumor-specific Mesorectal Excision

• June 2006 – December 2010, \( n = 370 \) rectal cancer patients

• Clinicopathologic and follow-up data recorded prospectively and analyzed retrospectively

Results

– 3-year overall survival rate 93.1%
– 3-year disease-free survival rate 79.2%
– 3-year cumulative local recurrence rate 3.6%

→ Robot-assisted tumor-specific mesorectal excision feasible and safe in terms of oncologic outcomes according to these data

Ongoing clinical trial - ROLARR

• Randomised controlled trial, $n = 400$ (planned)

• Laparoscopic surgery vs. robotic assisted laparoscopic surgery for rectal cancer

• **Primary outcome measure:**
  – Rate of conversion to open surgery

• **Secondary outcome measure:**
  – Oncological outcome (CRM positivity, 3-year local-recurrence rate)

• **Other outcome measures:**
  – Complications, 30-day mortality, 3-year disease-free and overall survival, sexual dysfunction assessment, QoL

Improvement in surgery for locally advanced rectal cancer

Options:

- Extended resection
- Improving functional outcome
- Robotic surgery
- **NIR fluorescence imaging**
- Auditing
- Organ preservation
NIR fluorescence imaging

• NIR fluorescence imaging has the potential to improve patient management

• Already feasible for a variety of intraoperative applications (>500 patients included in over 25 clinical studies)
  1. SLN mapping
  2. Tumor identification
  3. Identification of vital structures

• Future goals:
  • Improved (laparoscopic) imaging systems
  • Identify Biomarkers for imaging
  • Optimized NIR fluorescent probes
Why optical imaging?

- **Fast**: acquisition in milliseconds  
  - Real-Time and intraoperatively

- **Invisible to the human eye**  
  - No alteration of the surgical field

- Relatively **high tissue penetration** (~ 1 cm)
Focus Fluorescence-Guided Surgery

> 500 patients in more than 25 clinical trials
Tumor marking and SLN visualization in rectal cancer

- ICG injection endoscopically
- Fluorescence HD laparoscope
- Tumor “guidance” during resection
- Ex-vivo SLN mapping
Improvement in surgery for locally advanced rectal cancer

Options:

• Extended resection
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• Auditing
• Organ preservation
Audit

A quality instrument that collects detailed clinical data from different health care providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or MDT’s
Norwegian Quality Assurance Program – Rectal cancer


Sweden

post.op mortality %

annual no of op

Swedish cancer registry 2006
Sweden
Variability

<table>
<thead>
<tr>
<th></th>
<th>High-volume team</th>
<th>Low-volume team</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Mean no. of operations / year</td>
<td>&gt;12</td>
<td>0-12</td>
<td></td>
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<tr>
<td>Curative surgery</td>
<td>245 (78)</td>
<td>277 (82)</td>
<td></td>
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<tr>
<td>Median (range) of follow-up</td>
<td>41 (24-59)</td>
<td>43 (24-59)</td>
<td></td>
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<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local recurrence</td>
<td>9 (4)</td>
<td>27 (10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>39 (16)</td>
<td>54 (19)</td>
<td>0.33</td>
</tr>
<tr>
<td>Rectal cancer death</td>
<td>26 (11)</td>
<td>51 (18)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Martling et al, Br J Surg 2002;89:1008-13
The number of surgical departments treating rectal cancer decreased from 52 in 1994 to 26 by the end of 2006.
Audit

• Excellent results of national and regional audits

• However, differences in outcome between European countries remain
EURECCA
European Registration of Cancer care

- In 2007 initiated by ESSO/ECCO
- Foundation
- Legal entity
- Independent
- Non-profit
EURECCA – multidisciplinary cancer care

- Large database registry
- Observational population-based studies
- Data comparison: audit and quality assurance
- Identifying and communicating about ‘best practices’
- Consensus meeting, educational material and workshops
EURECCA
Frame of collaboration

ECCO
ESSO
ESMO
ESTRO
ESR, ESP
Scientific Societies

Cancer Registries Audits
Tumour groups
DATA & FEEDBACK

EURECCA Executive Board and managing staff
Changes in cancer treatment

- Empirical
- Stratified
- Personalised

- Multidisciplinary management

- Quality assurance

- Reduction under- and overtreatment
- Optimal care for every cancer patient
Change neoadjuvant treatment instead of intensifying surgery?

RAPIDO trial – inclusion criteria:

• Good quality MRI
• (T3 c/d), T4 a/b
• EMVI +
• N2
• N+ (outside the fascia plane)
• MRF +
RAPIDO trial

Experimental arm:
previous experience M1 Study

- 50 patients M1 (75% T3/4N+)
  5x5 Gy + XELOX + Bevacizumab (6 cycles) + surgery
- 83% received all chemo (90% ≥4 cycles)
  Low/acceptable toxicity
- pCR in 26% of specimens
  ‘No progression was seen on chemotherapy’

van Dijk et al. Annals of Oncology 2013
RAPIDO Trial – current status: 450 patients included

Locally advanced Rectal Cancer

Experimental Arm B:
5x5 Gy RT
Week 1

6 cycles of CAPOX
Week 3-18

Response evaluation by CT, and MRI
Week 21

Resectable:
Surgery
Week 22-24

Irresectable:
Palliative treatment

Standard arm A:
chemoradiotherapy
Week 1-6

Response evaluation by CT and MR
Week 12

Resectable:
Surgery
Week 14-16

Irresectable:
Palliative treatment

8 cycles of CAPOX
Week 20-41
Optional
Improvement in surgery for locally advanced rectal cancer

Options:

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Potential benefits of preoperative chemoradiation in rectal cancer

• Downstaging of the tumour

• Decreasing rates of positive surgical margins

• Improving local control

• Increasing sphincter-saving procedures

• May offer the possibility of sparing patients from postoperative morbidity associated with radical rectal surgery
Pathological outcome

• Complete remission!

Triumph or Tragedy?

• Is it possible to avoid unneeded resections?
Habr-Gama – Watch and Wait
Most recent publication

- Median FUP: 60 months

- 49% cCR after CRT (90/183 patients)

- 31% local recurrences (28/90 patients)
  - 26/28 salvage therapy, 2/28 patients not amenable to salvage

Observation after chemoradiation

Review

Critical appraisal of the ‘wait and see’ approach in rectal cancer for clinical complete responders after chemoradiation

R. Glynne-Jones and R. Hughes
Centre for Cancer Treatment, Mount Vernon Hospital, Northwood HA6 2RN, UK
Correspondence to: Dr R. Glynne-Jones (e-mail: rob.glynnejones@nhs.net)

• Habr-Gama series: low loco-regional failure rate (4.6%)
  • Supported by study of Maas et al.
  • Higher recurrence rates in other retrospective studies

• Heterogeneous studies in staging, inclusion criteria, study design and rigour of follow-up after CRT

• Inconsistent definition of cCR

Why the need of an international organ preservation database?

- Limited number of centers / patients

- No homogeneous staging, treatment or surveillance protocols

- Need for a network of interested clinicians & scientists

- Identify best practice patterns
Database Fields

- **Critical Data**
  - Minimal dataset
  - Tag patients
  - Characterizes center practice
  - Limiting point

- **Secondary Data**
  - More extensive information
  - Filled even retrospectively
  - Patient Outcome

- **Complete Data**
  - Complete description of treatment strategy
  - Doses/Protocols of RT and ChemoT
  - Could be filled anytime
Relevance prospective organ preservation database

• To study the concomitant risks-benefits

Per

• Age groups
• Comorbidity groups
• Tumour characteristics
• Chemoradiotherapy specifics
• Other adjustments
Relevance organ preservation database

- Provide evidence
- Help in protocol implementation
- Quality of care assessment
- Auditing
- Unit benchmarking

Educational Feedback

Data for Future Consensus Meetings

Incorporating W&W in Standard of Care
Per patient, 7 sections

A • Patient administrative data
• Comorbidities

B • Primary staging
• Biopsy, MRI, CT

C • Neoadjuvant
• Sort, toxicity

D • Antibody therapy

E • Restaging after CRT and surgery

F • Adjuvant treatment

G • Follow up
Is there still room for improvement in surgery for locally advanced rectal cancer?

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