Role of local excision for Rectal Cancer

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Catholic University of Leuven
Belgium
Organ sparing surgery in CRC not a new concept: renewed interest

- Bowel cancer screening programs (ERC)
- Awareness of morbidity (functional) after radical surgery (TME)
- Downstaging after neoadjuvant CRT
- New surgical techniques to perform ‘LE’
Bowel cancer screening and improved imaging

Chromo

HD

Fluorescence
Surgical technique

Trans-anal excision (TAE)

limited access and exposure
limited depth

Surgical technique

Trans – sacral (Kraske)
Trans – sphincteric (York-Mason)

violates mesorectal plane

important functional sequellae

Kraske P. Arch F Klin Chir (Berl) 1886; 33: 563-573
Transanal Endoscopic Microsurgery (TEM, 1983)

Surgical technique TEM

Posterior lesion  Anterior lesion  Lateral lesion
Endoluminal TAMIS (transanal minimally invasive surgery) using a adapted single-port device
TAMIS provides a stable (flexible) platform

<table>
<thead>
<tr>
<th></th>
<th>TEM</th>
<th>TAMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient position</td>
<td>tumor localization</td>
<td>lithotomy/prone</td>
</tr>
<tr>
<td>platform</td>
<td>rigid TEM-proctoscope 12 or 20 cm</td>
<td>Gelpoint Path ‘non-rigid’</td>
</tr>
<tr>
<td></td>
<td>adapted insufflator</td>
<td>standard insufflator high flow, &lt;15 mmHg Airseal°</td>
</tr>
<tr>
<td></td>
<td>specific 30° TEM-scope</td>
<td>5 or 10 mm 30° laparoscope</td>
</tr>
<tr>
<td>instruments</td>
<td>bended instruments</td>
<td>laparoscopic-instruments</td>
</tr>
<tr>
<td>surgeon</td>
<td>Single surgeon</td>
<td>Two surgeon</td>
</tr>
<tr>
<td>Investment</td>
<td>+++</td>
<td>none</td>
</tr>
</tbody>
</table>
What is the exact role of LE in early rectal cancer?
Appeal of organ preservation

Minimal perioperative morbidity and mortality
- bleeding
- anastomotic leak

Rapid recovery
Sphincter saving operation
Preservation of bowel function
- ‘anterior resection’ syndrome
- permanent colostomy

Preservation of urogential function
Improved QoL
Reduction in Health care cost
LE for T1 rectal cancer - NCDB
PERI-OPERATIVE OUTCOME

<table>
<thead>
<tr>
<th></th>
<th>LE</th>
<th>Rad R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.5%</td>
<td>1.0%</td>
<td>0.14</td>
</tr>
<tr>
<td>Morbidity</td>
<td>4.2%</td>
<td>13%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LOS (d)</td>
<td>1.9</td>
<td>8.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

J Clin Oncol 2005;23:16suppl: 3526
TAE for T1 rectal cancer


✓ in the RR group 20% lymph node metastasis

Nash GM. *Dis Colon Rectum* 2009; 52: 577-82
Case-matched pT1 TEM vs TME dutch trial data

De Graaf EJ et al. 
Failure of local excision (not only nodes...)

- untreated nodal disease
- inadequate resection margins
- tumour implantation at resection site
LNM in pT1
COLON or RECTAL ca

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIGHT COLON</td>
<td>3 %</td>
</tr>
<tr>
<td>LEFT COLON</td>
<td>8 % (4 – 13%)</td>
</tr>
<tr>
<td>RECTUM</td>
<td>15 %</td>
</tr>
</tbody>
</table>

*J Gastrointest Surg 2004;8: 1032 (MSKCC & Tokyo)*
LNM in pT1 – depth of submucosal invasion

<table>
<thead>
<tr>
<th>depth</th>
<th>n</th>
<th>n (%)N+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm1</td>
<td>70</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Sm2</td>
<td>120</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Sm3</td>
<td>154</td>
<td>35 (23%)</td>
</tr>
</tbody>
</table>

Nascimbeni R et al. *Dis Colon Rectum* 2002;45, 200-206
Clinicopathologic features of rectal cancer associated with nodal disease

<table>
<thead>
<tr>
<th></th>
<th>pN+(%)</th>
<th>pN-(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor differentiation</td>
<td>84.6%*</td>
<td>15.4%</td>
</tr>
<tr>
<td>LVI</td>
<td>72.4%*</td>
<td>27.6%</td>
</tr>
<tr>
<td>PNI</td>
<td>73.7%*</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

* $P<0.001$, chi-squared
### Failure of ERUS in nodal staging

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>pN+</th>
<th>size met</th>
<th>size node</th>
<th>ERUS accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1</td>
<td>21</td>
<td>29%</td>
<td>0.3</td>
<td>3.3</td>
<td>48</td>
</tr>
<tr>
<td>pT2</td>
<td>67</td>
<td>30%</td>
<td>4.1</td>
<td>6.2</td>
<td>67</td>
</tr>
<tr>
<td>pT3</td>
<td>44</td>
<td>46%</td>
<td>5.9</td>
<td>8.0</td>
<td>84</td>
</tr>
<tr>
<td>all</td>
<td>134</td>
<td>35%</td>
<td>4.9</td>
<td>6.5</td>
<td>70</td>
</tr>
</tbody>
</table>

MSKCC
Micro nodal metastasis
A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer

S. P. Bach¹, J. Hill², J. R. T. Monson³, J. N. L. Simson⁴, L. Lane⁵, A. Merrie⁷, B. Warren⁶ and N. J. McC. Mortensen⁵, on behalf of the Association of Coloproctology of Great Britain and Ireland Transanal Endoscopic Microsurgery (TEM) Collaboration

Risk stratification comes after the local excision.
Can we adequately stage T1?

20 – 25% understaging accuracy submucosal invasion?

and: c T1 was pT3, pT4 in about 20% (PROCARE)
Local recurrence (%) after LE + adjuvant (C)RT

<table>
<thead>
<tr>
<th></th>
<th>N patients</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>LE+RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LE</td>
<td>LE+RT</td>
</tr>
<tr>
<td>Chakravarti 1999</td>
<td>47</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Taylor 1998</td>
<td>34</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Varma 1999</td>
<td>23</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Lamont 2000</td>
<td>48</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Gopaul 2004</td>
<td>64</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Paty 2002</td>
<td>125</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

Limited data,
no reliable salvage

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clinical case (451016m054)

Male 57 yrs. uT1N0
TEM : pT1 sm3, gr 3, Lyv +
Adjuvant chemoradiation

Intensive FU : 5 years
yearly endoscopy

at 9 years: sciatic pain +++

at 10 years: lung – liver metastasis
Completion radical resection does not compromise oncological results

**Mayo data**

Stage -matched cohort (n=52)

Completion radical = primary RR

**Mainz data**

Completion radical for pT2 = primary RR

Local excision vs Completion radical in High risk ERC

Early TME after TEM

UK TEM database, courtesy by Mr C. Cunningham
Salvage Surgery for recurrence after local excision: failure of surveillance

50 - 80% undergo salvage

50% extended pelvic resection

5 yr survival

salvage: ± 50%

radical surgery in pT1: 94%

Ann Surg 2002; 236: 522
Disease Colon Rectum 2005; 48: 1169
## Salvage Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>recurrence</th>
<th>LR</th>
<th>Pelvic salvage</th>
<th>FU (mo)</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paty et al. MSKCC 2002</td>
<td>125</td>
<td>27%</td>
<td>68%</td>
<td>41%</td>
<td>80</td>
<td>50%</td>
</tr>
<tr>
<td>Benson et al. 2001</td>
<td>73</td>
<td>32%</td>
<td>89%</td>
<td>57%</td>
<td>48</td>
<td>23%</td>
</tr>
<tr>
<td>Mellgren et al. Minnesota 2000</td>
<td>108</td>
<td>25%</td>
<td>93%</td>
<td>89%</td>
<td>53</td>
<td>50%</td>
</tr>
</tbody>
</table>
LE in early rectal cancer

- Cures pT1 sm1,2 well, moderate differentiated without lymphovascular invasion

- Radical completion surgery after excisional biopsy is required for unfavourable histology
Can we avoid radical surgery in good responders after chemoradiotherapy?

concept of sustained clinical complete response
role for local excision after chemoradiation?
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 Nadalin, MD,† Jorge Sabbaga, 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‡

Watch and Wait Algorithm

- Patients with Distal Rectal Cancer (< 7 cm from anal verge)
- Neoadjuvant CRT
- 8 week Followup
- Digital Rectal Examination
- Rigid Proctoscopy
- Biopsy of suspicious lesion
- CEA level

N = 265 pts

N = 22 pts (8.3%) pCR

N = 71 pts (26.8%) sustained cCR

0S

DFS

....observation__radical surgery

Complete clinical response (Habr Gama)
inter observer variablity ?

- careful digital examination

- proctoscopy
  - whitening of mucosa
  - teleangiectasia
  - loss of plicability of rectal wall

Habr-Gama et al.  
*Dis of Colon Rectum* 2010;53:1692-1698
Predictive value of clinical complete response (ccR)

n= 488 patients
Memorial Sloan Kettering

ccR = 19%

cpR = 10%

ccR = predictive factor for cpR

but:

75% of ccR : residual foci of tumor
Distribution of Residual Cancer Cells in the Bowel Wall After Neoadjuvant Chemoradiation in Patients With Rectal Cancer

Marjun P. Duldulao, M.D.¹ • Wendy Lee, B.A.¹ • Leanne Streja, Dr.P.H.²
Peiguo Chu, M.D.³ • Wenyan Li, B.A.¹ • Zhenbin Chen, Ph.D.¹
Joseph Kim, M.D.¹ • Julio Garcia-Aguilar, M.D., Ph.D.⁴

Response is heterogeneous in the tumor

Significant no of advanced cancers do not have residual cancer cells in mucosa, submucosa after chemoradiation

Dis Colon Rectum 2013
Can biopsies rule out persisting cancer in incomplete clinical response?

**PPV = 100%**

**NPV = 21%**

**Accuracy = 71%**

<table>
<thead>
<tr>
<th>Biopsy finding</th>
<th>Incomplete histopathological response</th>
<th>Complete histopathological response</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>3</td>
<td>39</td>
</tr>
</tbody>
</table>

Perez RO et al. *Colorectal Dis* 2012
Significance of residual mucosal abnormalities?

61% (19/31) with cPR had an incomplete cR

<table>
<thead>
<tr>
<th>mucosal lesion</th>
<th>ypT0</th>
<th>ypT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1cm</td>
<td>42%</td>
<td>27%</td>
</tr>
<tr>
<td>1-2cm</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>&gt; 3cm</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

“clinical” complete response after chemo-radiation and long interval

“wait and see”

TAE/TEM/TAMIS
(full-thickness local excision)

late failures

sustained cCR

ypT0

yp≥T1

late failures

delayed radical surgery

close follow-up

radical surgery
TEM after RCT in uT2-T3 N0 < 3 cm

Local failure rate: 5%
55 m (7-120 mo)
% (90 months)

Overall Survival: 72%

### Pooled data on TEM after neo-adjuvant chemoradiotherapy

<table>
<thead>
<tr>
<th>yp T0</th>
<th>n = 53</th>
<th>22 %</th>
<th>0%</th>
<th>4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>yp T1</td>
<td>n = 45</td>
<td>19 %</td>
<td>2 %</td>
<td>7%</td>
</tr>
<tr>
<td>yp T2</td>
<td>n = 85</td>
<td>36 %</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>yp T3</td>
<td>n = 34</td>
<td>14 %</td>
<td>21%</td>
<td>12%</td>
</tr>
</tbody>
</table>

6 retrospective studies, 1 prospective study

LE after chemoradiation: the technique?

What margins?

= excisional biopsy to further tailor treatment (avoid to jeopardise CRM if completion is needed)
Morbidity TEM after neoadjuvant chemoradiation therapy

<table>
<thead>
<tr>
<th></th>
<th>Study group (neoadjuvant CRT) N=23</th>
<th>Control group N = 13</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I morbidity</td>
<td>52%</td>
<td>13%</td>
<td>0.030</td>
</tr>
<tr>
<td>Grade II/III</td>
<td>56%</td>
<td>23%</td>
<td>0.050</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>70%</td>
<td>23%</td>
<td>0.030</td>
</tr>
<tr>
<td>Hospital readmission</td>
<td>43%</td>
<td>7%</td>
<td>0.020</td>
</tr>
<tr>
<td>Late complications</td>
<td>4%</td>
<td>15%</td>
<td>0.25</td>
</tr>
<tr>
<td>Interval to healing</td>
<td>8 (5-12) weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Local Excision After Preoperative Chemoradiotherapy for Rectal Cancer: Results of a Multicenter Phase II Clinical Trial

Salvatore Pucciarelli, M.D.¹ • Antonino De Paoli, M.D.² • Mario Guerrieri, M.D.³
Giuseppe La Torre, M.D.⁴ • Isacco Maretto, M.D.¹ • Francesco De Marchi, M.D.⁵
Giovanna Mantello, M.D.⁶ • Maria Antonietta Gambacorta, M.D.⁷
Vincenzo Canzonieri, M.D.⁸ • Donato Nitti, M.D.¹ • Vincenzo Valentini, M.D.⁷
Claudio Coco, M.D.⁹

Kaplan-Meier survival estimate

disease free survival

Dis Colon Rectum 2013
Ongoing trials

Greccar II : distal rectal cancer <4cm
   TAE after CRT (in responders) versus radical surgery

TREC : early rectal cancer (cT1-cT2)
   TEM after SCRT and interval versus radical surgery

CARTS : early rectal cancer (cT1-cT2)
   LE in clinical responders (MRI) vs radical surgery
How do we organise surveillance?

Digital examination
Endoscopy

Imaging
MRI
DW-MRI
PET

Interval
Duration
Microarray-based prediction of Tumor response to neo-adjuvant radiochemotherapy

Hierarchical clustering
50 sign diff expressed probe sets: 42 genes

Principal component analysis plot
Prelim gene select (p<0.001)

Rimkus C. et al.
Clin Gastroenterol and Hepatol 2008;6:53-61
Towards a patient/tumor tailored approach

- Local excision for pT1sm1,2, LyV-

- exact role local excision after neoadjuvant treatment in localised rectal cancer needs to be established