TUMOR REGRESSION GRADING OF GASTROINTESTINAL CARCINOMAS – ANYTHING NEW?

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No conflicts of interest to declare
Male patient, 65 years
Adenocarcinoma distal Esophagus, St.p. neoadjuvant RCTX
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Adenocarcinoma distal Esophagus, St.p. neoadjuvant RCTX

- Good morphological response
- Few residual tumor cells present in deeper layer of the esophageal wall
- Lymph node with regressive changes (no residual tumor)
- ypT3 N0 (0/23) L0, V0, R0
- TRG 1b (Becker), <10% residual tumor
- LN status?
Tumor Regression Grading

• Estimates the degree of regressive changes of the primary tumor basing on histology
• Routinely performed for >20 years for esophageal, gastric and rectal cancer
• Prognostic value
  – Initial reports and subsequent larger studies including meta-analyses and clinical trials (see references)
• substantial interobserver agreement
  – only few studies, mostly one particular system (ref)
• Valuable and reliable «biomarker»
• Different grading systems
  • Various practices world wide
  • Consensus needed before final recommendation and implementation into TNM staging

- Cunningham et al. 2017 (UK ST03); 1063pts. p<0.0001*
- Alderson et al. 2017 (UK OE05); 897pts; p=0.028; p<0.0001*
- Noble et al. 2017 (Multicenter Study), 1392 pts. p<0.001*
- Smyth et al. (MAGIC); 330 pts. p=0.02*
- Al-Batran et al. (FLOT-AIO) 2016; 300pts. p<0.001**
- Tomassello et al. 2017 (Meta-A; 17 studies; 3145 pts.), p<0.0001
- Spoerl et al. (AIO, Multicenter); 461pts. p=0.031 (intestinal T)**
- Fokas et al. 2017, (CAD/ARO/AIO); 1179 pts. p<0.001***
- Kim et al. 2017 (prognosis and interobserver; single center), 933 pts. p<0.001****
- Karamitopoulou et al., 2014 (interobserver)
Frequently used TRG systems

<table>
<thead>
<tr>
<th>Becker</th>
<th>AJCC/Ryan</th>
<th>Mandard</th>
<th>Dworak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a: no residual tumor/tumor bed + chemotherapy effect</td>
<td>0: no residual tumor cells</td>
<td>1: complete regression (= fibrosis without detectable tissue of tumor)</td>
<td>4: no vital tumor cells detectable</td>
</tr>
<tr>
<td>1b: &lt; 10% residual tumor/tumor bed + chemotherapy effect</td>
<td>1: single cells or small groups of cells</td>
<td>2: fibrosis with scattered tumor cells</td>
<td>3: only scattered tumor cells in the space of fibrosis with/without acellular mucin</td>
</tr>
<tr>
<td>2: 10-50% residual tumor/tumor bed + chemotherapy effect</td>
<td>2: residual cancer with desmoplastic response</td>
<td>3: fibrosis and tumor cells with preponderance of fibrosis</td>
<td>2: predominantly fibrosis with scattered tumor cells (slightly recognizable)</td>
</tr>
<tr>
<td>3: &gt; 50% residual tumor/tumor bed +/- chemotherapy effect</td>
<td>3: minimal evidence of tumor response</td>
<td>4: fibrosis and tumor cells with preponderance of tumor cells</td>
<td>1: predominantly tumor with significant fibrosis and/or vasculopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5: tissue of tumor without changes of regression</td>
<td>0: no regression</td>
</tr>
</tbody>
</table>

Residual tumor in % or descriptive

Residual tumor vs. Fibrosis

Each of them initially described for one particular entity (and one particular therapy) but can be used interchangeably.
TUMOR REGRESSION GRADING OF GASTROINTESTINAL CARCINOMAS – ANYTHING NEW?

Part I Comprehensive survey on TRG among GI pathologists
Part II Impact of regressive changes in LN Metastases
Part I - Varying Practices in Tumor Regression Grading of Gastrointestinal Carcinomas - Results of a World Wide Survey

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\textsuperscript{2}Institute of Pathology, University of Bern, Switzerland
Conduction of the World Wide Survey

- Target: GI pathologists / Pathologists with particular interest in GI
- First public announcement at USCAP 2018
- Second public announcement at ECP 2018 (assembly of the GI WG)
- Distribution via pathology and disease focused societies and by personal invitations and further distribution
- May 2018 – February 2019
- Topics: Work up, TRG reporting practice, difficulties, general opinions and recommendations
Results - Demographics

- Participants: 203
- 173 completed survey
- 50% >20 GI cases treated with nTX/year
- 66% >10 years experience
- 70% Academic Centers
- World wide survey
  - All continents
  - Europe > North America > Rest
**Work up - Macro/Histo**

Do you use a standardized protocol for the work up of resection specimens?

- Yes: 100%
- No: 0%

How many blocks do you submit of the tumor bed in a post-neoadjuvant resection case?

- up to 3 blocks: 0%
- several blocks (>3): 10%
- complete, up to certain size: 60%
- always completely: 30%

HE only: 60%
HE and special stains: 17%
HE and IHC: 23%
Which TRG system do you use for...?
Which TRG system do you use for...? (North America)
Which TRG system do you use for...? (Europe)
Varying practices in tumor regression grading of gastrointestinal carcinomas after neoadjuvant therapy

- North America vs. Europe
- within Europe
  - North/West
  - Central
  - South/East

- Among the different entities
  (e.g. Dworak: rectal cancer; Becker Gastric Cancer)
How would you rate the degree of difficulty in carrying out..

- estimation of residual tumor
- estimation of therapy-induced fibrosis
- identification of residual tumor
- interpretation of mucin (acellular or paucicellular)

Rating options:
- very easy
- easy
- neutral
- difficult
- very difficult
How important would you rate...?

- Standardized grossing
- Standardized histology work up
- Standardized reporting of TRGs (each tumor entity separately)
- Standardized reporting of TRGs (the same for all gastrointestinal cancers)

0% 10% 20% 30% 40% 50% 60% 70% 80%

- not at all important
- slightly important
- neutral
- moderately important
- very important
The ideal TRG system...?

How many tiers do you think is it reasonable for a TRG system?

Which parameters would you recommend a TRG system on GI cancers to be based on?
Free Comments

• TRG as “pseudo science” .. *The simplier the better*
• Relation to *pre-therapeutic conditions* (e.g. tumor volume, stroma content etc.)
• Demand of data driven recommendations
• discrepancy with radiological assessment of tumour regression
• lot of extra work without *consequence*?
• Problem of stroma rich tumors (e.g. diffuse type gastric cancers)
• Necessity to closely work together with *medical oncologists*, who actually use and act on the grade.
• Careful selection of wording and ranking (best grade for degree of regression or residual tumor)
• One system across the luminal gut
• Consider *USUAL clinical practices* – vs. academics
• *Consider costs vs. benefit* (i.e. clinical consequence)
Summary – Part I

• Standardized work up
• Standardized reporting
  - Including the application of a TRG

• High variety of TRG systems used
  • North America: AJCC/CAP
  • Europe: Mandard, Becker, Ryan, Dworak, others..
  • Organ specific (esophageal – gastric – rectal cancers)

• Good system: favor 4 tiers
• No agreement on what should be the base of TRG
• ..clinical consequences?
And now?
Mandard vs. Becker

MANDARD

- TRG 1: complete regression
- TRG 2: rare residual cancer cells scattered through fibrosis
- TRG 3: increased number of residual cancer cells, but fibrosis still predominates
- TRG 4: shows residual cancer outgrowing fibrosis
- TRG 5: absence of regressive changes.

BECKER

- TRG 1a: complete regression
- TRG 1b: <10% residual tumor
- TRG 2: 10-50% residual tumor
- TRG 3: >50% residual tumor

- Mandard (with combined TRG4 and 5) similar to AJCC/CAP/Ryan
- Cut-off for «subtotal» regression are different to Becker’s 10% (1%? 5%?)
  (also used in the Cologne/MD Anderson)
Which System? Mandard vs Becker – survival
(Bern Cohort, Esophageal cancer; n=199; neoadjuvant RXTC)
Outlook – Part I

• Lack of data comparing the different systems
• Lack of clearly defined problems (e.g. what to do with poorly cohesive GC?)
  • (Re)assessment of case collections, preferably from clinical trials (ongoing)
  • Prognostic relevance (and differences) of the various systems
  • Interobserver agreement (improves with clear definition of criteria)
• Discussion within workshops and expert rounds (e.g. ICCR, IGCA, ongoing), but the opinions of the colleagues should be taken into account
• Development of clear criteria (wording) for the assessment of TRG
• Is this all clinically relevant? - ask surgeons and medical oncologists
• One fits all?
Part II Tumor Regression in Lymph Nodes

ypN0
- Inflammation
- necrosis
- Fibrosis
- Hyalinosis
- Hemosiderin
- Histiocytes
- Cholesterol clefts
- Single (viable?) tumor cells

ypN1

in some cases divergent regression between primary tumor site and LN may be observed (i.e. ypT0, L1, N1)
Do you believe it is important to mention tumor regression changes that are found in lymph nodes in your report?

- Not particularly: 0%
- Yes (presence or absence): 70%
- Yes (including grading): 10%

Should regressive changes in lymph node/lymph node metastases be part of a regression grading system?

- Yes: 50%
- No: 50%
Lymph nodes and regressive changes
preliminary results from 480 gastric cancer cases

• Well characterized case cohort (Ann Surg 2011 and 2012)
• Including 177 GE junction cases (AEG II)
• LN count 4 to 147 (median=30)
• Presence or absence of regressive changes in one or more LN
  (regardless how many)*
• Comparison with TRG, other pathological parameters and outcome
  (overall survival)

*Tsekretos et al., 2019; Zhu et al. 2019
Lymph nodes and regressive changes
preliminary results from 480 gastric cancer cases

<table>
<thead>
<tr>
<th>ypN0 status</th>
<th>No regressive changes</th>
<th>Regressive changes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypN0 no regressive changes</td>
<td>139</td>
<td>29.0%</td>
<td></td>
</tr>
<tr>
<td>ypN0 regressive changes</td>
<td>28</td>
<td>5.8%</td>
<td></td>
</tr>
<tr>
<td>ypN1-3 regressive changes</td>
<td>100</td>
<td>20.8%</td>
<td></td>
</tr>
<tr>
<td>ypN1-3 no regressive changes</td>
<td>213</td>
<td>44.4%</td>
<td></td>
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Total 480 100.0%

Reim et al., in preparation

128/480 cases 26.6%
# Lymph nodes and regressive changes

Correlation with TRG of the primary tumor

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<td>2</td>
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<tr>
<td>ypN0 no regressive changes</td>
<td>10</td>
<td>40</td>
<td>37</td>
<td>52</td>
<td>139</td>
</tr>
<tr>
<td>ypN0 regressive changes</td>
<td>3</td>
<td>17</td>
<td>6</td>
<td>2</td>
<td>28</td>
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<tr>
<td>ypN1-3 regressive changes</td>
<td>3</td>
<td>13</td>
<td>46</td>
<td>38</td>
<td>100</td>
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<tr>
<td>ypN1-3 no regressive changes</td>
<td>0</td>
<td>16</td>
<td>32</td>
<td>165</td>
<td>213</td>
</tr>
<tr>
<td>total</td>
<td>16</td>
<td>86</td>
<td>121</td>
<td>257</td>
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## Lymph nodes and regressive changes

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p<0.001
Lymph nodes and regressive changes

survival analysis

P<0.001

LN_REG_Q

P<0.001
Lymph node regression and survival following neoadjuvant chemotherapy in oesophageal adenocarcinoma

A. R. Davies1,3,10, D. Myoteri2, J. Zylstra1,3,8, C. R. Baker1,3, W. Wulaningsih4, M. Van Hemelrijck4,5, N. Maisey5, W. H. Allum6, E. Smyth6, J. A. Gossage1,3,8, J. Lagergren1,3,8, D. Cunningham6,7 and M. Green2, on behalf of the Guy’s and St Thomas’ Oesophago-Gastric Research Group and PROGRESS Study Group

Departments of Surgery and Cellular Pathology, Guy’s and St Thomas’ Oesophago-Gastric Centre, Gastrointestinal Cancer and Translational Oncology and Urology Research, School of Cancer Sciences, King’s College London, Department of Oncology, Guy’s Cancer Centre, Guy’s Hospital, Department of Oncology, Royal Marsden Hospital, and Institute of Cancer Research, London, UK, and Upper gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden.

Correspondence to: Mr A. Davies, Department of Surgery, St Thomas’ Hospital, London, UK (e-mail: andrew.davies@sth.nhs.uk)

Fig. 3 Kaplan–Meier analysis of a overall and b disease-free survival in lymph node responders (LN-R) versus non-responders (LN-NR). a P < 0.001, b P < 0.01 (log rank test)

Fig. 4 Kaplan–Meier analysis of overall survival according to node status: a N0–N2, including patients downstaged from N1–2 to N0, and b N1–N3, including patients downstaged from N2–3 to N1. a P < 0.001, b P < 0.015 (log rank test)
403 patients
Esophageal Cancer, RCTX

High regression = ypN0 without or 1-2 LN with regression

Medium regression = ypN0 with and 3 or more LN with regression or LNmets with an LN ratio of less than 0.05

Low regression = all other cases
Summary Part II

• Tumor regression occurs in around 30% of lymph node (metastases)
• Some evidence of prognostic impact
  – Always negative LN vs. LN Mets with complete regression
  – LN Mets with regression vs. LN Mets without regression
• Absence or presence vs. grading?
• Impact of the number of nodes with/without changes
• More data are necessary
Thank you

All participants of the survey around the World
Support of the Gastrointestinal Working Group ESP, AG Gastrointestinale Pathologie DGP, OESO, US/CAN, SAGIP