Classic prognosticators do not adequately predict oncologic outcome after rectal cancer resection

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CONFLICT OF INTEREST

The authors have no disclosures
Introduction: rectal cancer and prognosis

- Numerous prognostic factors described:
  - ASA score, TNM, lymph node ratio, CEA, age, TME quality, resection margins

- Emphasis on pCRM and TME quality

- Relative importance of risk factors and effect-size poorly known

Background & Aim

• Hypothesis:
  Clinical and pathological risk factors of oncologic outcome have different levels of importance and their impact on outcome can be weighted.

• Aim:
  Determine the individual, unique and relative contributions or effect-size of known patient-, tumor and treatment-based variables to oncologic prognosis.
Patients and Method

- Procare patient: Belgian national rectal cancer care improvement program
- Between 2006 and 2011
- TME only: 0 to 10 cm from anal verge
- Stage IV excluded
- 1470 patients
Patients and Method

• Univariable and multivariable models
• Cox proportional hazard
• Forward model selection
• CPE and the pseudo R-square value were used for evaluating the accuracy of models
• Oncologic outcomes: local/distant, overall recurrence and overall survival
• Individual, unique and relative contributions determined for each variable
## Patients and Method

<table>
<thead>
<tr>
<th>Gender</th>
<th>N quadrants (2 cat.)</th>
<th>pStage</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>1-2</td>
<td>0/I</td>
</tr>
<tr>
<td>Female</td>
<td>3-4</td>
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</table>

<table>
<thead>
<tr>
<th>Neoadjuvant treatment</th>
<th>ASA 1</th>
<th>ASA 2</th>
<th>ASA &gt;=3</th>
<th>BMI, Mean (SD)</th>
<th>LLcm, Mean (SD)</th>
<th>cT</th>
<th>cN</th>
<th>cStage</th>
<th>CEA</th>
<th>Extramural tumor deposits</th>
<th>Extramural vascular invasion</th>
<th>Adjuvant chemotherapy</th>
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<tbody>
<tr>
<td>No</td>
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<td></td>
<td></td>
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<td>N0</td>
<td>0/I</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>T2</td>
<td>N1</td>
<td>II</td>
<td></td>
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<td>N2</td>
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<table>
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<tr>
<th>Surgical approach for TME</th>
<th>Type of radical resection</th>
<th>Intra-operative perforation</th>
<th>Peri-operative blood transfusion</th>
<th>TME quality</th>
<th>Tumor diameter (2 cat.)</th>
<th>pT</th>
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<tbody>
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<td>Open</td>
<td>APER</td>
<td>No</td>
<td>No</td>
<td>Mesorectal plane</td>
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<td>T0-T2</td>
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<td>(Converted) Laparoscopy</td>
<td>SSO/Hartmann</td>
<td>Yes</td>
<td>Yes</td>
<td>Intramesorectal plane</td>
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<td>T3-T4</td>
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<table>
<thead>
<tr>
<th>Cell differentiation</th>
<th>Margin positivity</th>
<th>Lymph Node Ratio, Mean (SD)</th>
<th>Extramural vascular invasion</th>
<th>Adjuvant chemotherapy</th>
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<tbody>
<tr>
<td>Well</td>
<td>No</td>
<td></td>
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<td>No</td>
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<td>Moderate</td>
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<tr>
<td>Poor</td>
<td></td>
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<table>
<thead>
<tr>
<th>Ventral tumor location</th>
<th>N Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Involved</td>
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</table>


Patients and Method

• Individual contribution
  – defined as the pseudo R-square of its univariable model

• Unique contribution
  – extent to which variation is uniquely explained by this predictor and not by any other predictor

• Relative contribution
  – respective contribution when unexplained variability was ignored
Patients and Method

Variability of the outcome of interest

Prognostic factor explaining part of the outcome variability
Patients and Method

Variability of the outcome of interest

Prognostic factor explaining part of the outcome variability

INDIVIDUAL CONTRIBUTION
Patients and Method

Variability of the outcome of interest

Prognostic factor explaining part of the outcome variability

INDIVIDUAL CONTRIBUTION
Patients and Method

Variability of the outcome of interest

Prognostic factor explaining part of the outcome variability

INDIVIDUAL CONTRIBUTION

OVERLAP
Patients and Method

Variability of the outcome of interest

Prognostic factor explaining part of the outcome variability

INDIVIDUAL CONTRIBUTION

OVERLAP

UNIQUE CONTRIBUTION
Patients and Method

Variability of the outcome of interest

Prognostic factor explaining part of the outcome variability

INDIVIDUAL CONTRIBUTION

OVERLAP

UNIQUE CONTRIBUTION

UNPREDICTED
Patients and Method

Variability of the outcome of interest

Prognostic factor explaining part of the outcome variability

RELATIVE CONTRIBUTION

INDIVIDUAL CONTRIBUTION

OVERLAP

UNIQUE CONTRIBUTION

UNPREDICTED
Results

- 5-year
  - local recurrence rate: 4%
  - Distant metastasis rate: 21%
  - Overall recurrence rate: 23%
  - Overall survival: 76%

- Unique contributions of variables ranging from 0.1% to 3.1%

- Large amount of variability unexplained ranging from 83.6% to 84.7%
Results

Multivariable Analysis
Local Recurrence

• Low number of events : n=35
• Unstable model

→ Decision not to perform analysis
Unique (A) & Relative (B) contribution
- Distant Metastasis
Unique (A) & Relative (B) contribution - Overall Recurrence

A
- Unexplained (84.7 %)
- TME quality (0.6 %)
- Overlap (9.3 %)
- LNR (2.6 %)
- OTHER
- Age (0.9 %)
- pT (1.0 %)

B
- LNR (17.1 %)
- Extramural vascular invasion (0.0 %)
- Extramural tumour deposits (1.4 %)
- Age (5.9 %)
- pT (6.3 %)
- pStage (3.1 %)
- Type of radical resection (1.5 %)
- TME quality (3.9 %)
- Overlap (60.6 %)
Unique (A) & Relative (B) contribution - Overall Survival

A

Unexplained (83.6 %)

B

Age (19.1 %)
Extramural tumour deposits (1.5 %)
Extramural vascular invasion (2.2 %)
LNR (8.2 %)
Margin positivity (3.7 %)
Overlap (40.5 %)
TME quality (7.1 %)
Tumor diameter (3.4 %)
pT (6.0 %)
ASA (8.2 %)

Overall Survival

ASA (1.3 %)
Age (3.1 %)
LNR (1.4 %)
Margin positivity (0.6 %)
Overlap (6.6 %)
TME quality (1.2 %)
Unexplained (83.6 %)
pT (1.0 %)
Discussion

• A very large amount of outcome variability remains unexplained
  – Need for other predictive factors like genetic or immune variables
    Hartnett et al., Carcinogen 2012; Jass et al., Surg Oncol 2007;
    Fridman et al., Nature Cancer Rev 2012; Galon et al., Science 2006

• Study regarding node negative breast cancer similar poor predictive value of outcome
  De Graf et al., Statistics in Medicine 1999

• Weaknesses of the study
  – Retrospective study
  – Voluntary participation: registration bias
Conclusions

Patient-, tumor- and treatment-related variables predict about one fifth of the oncologic outcome after curative resection of mid and low rectal cancer

A very large amount of outcome variability remains unexplained

These findings suggest the interest of exploring the additional contribution of variables not included in this, and many other studies