PATHOLOGIC FACTORS PROGNOSTIC OF SURVIVAL IN PATIENTS WITH GI TRACT AND PANCREATIC CARCINOMA TREATED WITH NEOADJUVANT THERAPY

Jeannelyn S. Estrella, MD
Department of Pathology
The UT MD Anderson Cancer Center
ESOPHAGEAL ADENOCARCINOMA
ESOPHAGEAL ADENOCARCINOMA

MD Anderson
• N=235 + neoadjuvant chemoXRT

ypTNM (AJCC 6th)
## Results of Multivariate Cox Regression Analysis of Disease-Free Survival and Overall Survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients (n = 235) (%)</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR  (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Extent of residual carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% (reference)</td>
<td>77 (33)</td>
<td>1.00 (0.40–4.79)</td>
<td>0.61</td>
</tr>
<tr>
<td>1–10%</td>
<td>50 (25)</td>
<td>1.39 (0.32–4.09)</td>
<td>0.83</td>
</tr>
<tr>
<td>11–50%</td>
<td>43 (18)</td>
<td>1.15 (0.67–7.87)</td>
<td>0.19</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>57 (24)</td>
<td>2.29 (0.67–7.87)</td>
<td></td>
</tr>
<tr>
<td>Pathologic [ypTNM] stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (reference)</td>
<td>69 (29)</td>
<td>1.00</td>
<td>0.02</td>
</tr>
<tr>
<td>I</td>
<td>25 (11)</td>
<td>0.92 (0.22–3.78)</td>
<td>0.90</td>
</tr>
<tr>
<td>II</td>
<td>80 (34)</td>
<td>1.06 (0.31–3.67)</td>
<td>0.93</td>
</tr>
<tr>
<td>III</td>
<td>46 (20)</td>
<td>2.03 (0.50–8.28)</td>
<td>0.32</td>
</tr>
<tr>
<td>IV</td>
<td>15 (6)</td>
<td>3.89 (0.85–17.71)</td>
<td>0.08</td>
</tr>
<tr>
<td>Downstage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>103 (44)</td>
<td>1.00</td>
<td>0.65</td>
</tr>
<tr>
<td>Yes</td>
<td>132 (56)</td>
<td>1.16 (0.61–2.19)</td>
<td></td>
</tr>
<tr>
<td>Any margin positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>211 (90)</td>
<td>1.00</td>
<td>0.12</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (10)</td>
<td>1.59 (0.83–2.86)</td>
<td></td>
</tr>
</tbody>
</table>

HR: hazard ratio; 95% CI: 95% confidence interval; ypTNM: posttherapy pathologic tumor/lymph node/metastasis stage.
MD Anderson
- N=187 +neoadjuvant chemoXRT

**Number of +LN**

*Cancer. 2006 Mar 1;106(5):1017-25*
ESOPHAGEAL ADENOCARCINOMA

Memorial Sloan-Kettering
- N=276 + neoadjuvant chemoXRT
- Kaplan-Meier analyses:
  - 0 to IIA (P=0.52)
  - IIB to III (P=0.87)
  - IVA to IVB (P=0.30)

Fig 1. American Joint Committee on Cancer (AJCC) staging system after chemoradiotherapy.

ypTNM (AJCC 6th)

J Clin Oncol. 2007 Feb 10;25(5):507-12
Memorial Sloan-Kettering
- N=276 + neoadjuvant chemoXRT
- Best predictors LN status metastasis

**ESOPHAGEAL ADENOCARCINOMA**

**Fig 4.** Recursive partitioning using TNM and number of positive lymph nodes (LN) as variables.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>No. of deaths</th>
<th>T</th>
<th>No. of positive LN</th>
<th>M</th>
<th>Hazard rate</th>
<th>3-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>92</td>
<td>30</td>
<td>0-1</td>
<td>0-1</td>
<td>0</td>
<td>0.59</td>
<td>70.3</td>
</tr>
<tr>
<td>B</td>
<td>87</td>
<td>36</td>
<td>2-4</td>
<td>0</td>
<td>0</td>
<td>0.78</td>
<td>52.4</td>
</tr>
<tr>
<td>C</td>
<td>20</td>
<td>12</td>
<td>2-4</td>
<td>1</td>
<td>0</td>
<td>1.25</td>
<td>32.2</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>8</td>
<td>0-4</td>
<td>0-1</td>
<td>1</td>
<td>2.06</td>
<td>11.3</td>
</tr>
<tr>
<td>E</td>
<td>53</td>
<td>36</td>
<td>0-4</td>
<td>≥ 2</td>
<td>0</td>
<td>1.73</td>
<td>26.3</td>
</tr>
<tr>
<td>F</td>
<td>14</td>
<td>12</td>
<td>0-4</td>
<td>≥ 2</td>
<td>1</td>
<td>3.78</td>
<td>0</td>
</tr>
</tbody>
</table>
2 high-volume centers in London
- N=584 patients
- N=400 + neoadjuvant tx
- Downstaging:
  HR=0.43, 95%CI 0.31-0.59
  strongest independent predictor

Tumor downstaging

ESOPHAGEAL ADENOCARCINOMA

Neuroendocrine differentiation

Cancer. 2006 Oct 1;107(7):1467-74
GASTRIC CARCINOMA
GASTRIC CARCINOMA

Margin status, pathologic response

MD Anderson
- N=41 + neoadjuvant chemoXRT
  localized gastric ca

<10% residual tumor

J Clin Oncol. 2005 Feb 20;23(6):1237-44
GASTRIC CARCINOMA

MD Anderson
- N=69 + neoadjuvant chemoXRT localized gastric ca

AJCC stage (6th)
GASTRIC CARCINOMA

TRG1 <10%, TRG2 10-50%, TRG3 >50%

Technische Universität München
- N=440 +neoadjuvant chemo
  locally advanced gastric ca

Pathologic response, LN status

UICC 2002 ypN

PANCREATIC DUCTAL CARCINOMA
MD Anderson
• N=240 +neoadjuvant chemoXRT

AJCC stage (7th)

ypN1a: 1-3 +LN, ypN1b: >3 +LN

Cancer. 2012 Jan 1;118(1):268-77
MD Anderson
- N=225 patients + neoadjuvant chemoXRT

PV/SMV involvement

Cancer. 2012 Aug 1;118(15):3801-11
MD Anderson
• N=212 patients + neoadjuvant chemoXRT

+Muscular vessel
Pathologic response

- MD Anderson
- N=223 + neoadjuvant chemXRT

Group 1: <5%, Group 2: ≥5%

Cancer. 2012 Jun 15;118(12):3182-90
RECTAL CARCINOMA
RECTAL CARCINOMA

CAO/ARO/AIO-94 trial (multicenter randomized phase III study)
- N=402 +neoadjuvant chemoXRT
- Median follow-up: 132 months
- TRG: 0-no response, 1-≤25% fibrosis, 2-26-50% fibrosis, 3->50% fibrosis, 4-complete response
Table 1: Definitions of categories within tumour regression grading (TRG) systems.

<table>
<thead>
<tr>
<th>System</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandard five-point TRG system [7]</td>
<td></td>
</tr>
<tr>
<td>TRG 1</td>
<td>(Complete regression) with absence of residual cancer and fibrosis extending through the wall</td>
</tr>
<tr>
<td>TRG 2</td>
<td>Presence of rare residual cancer cells scattered through the fibrosis</td>
</tr>
<tr>
<td>TRG 3</td>
<td>An increased number of residual cancer cells, but fibrosis is still predominant</td>
</tr>
<tr>
<td>TRG 4</td>
<td>Residual cancer outgrowing fibrosis</td>
</tr>
<tr>
<td>TRG 5</td>
<td>Absence of regressive changes</td>
</tr>
<tr>
<td>RCPaht system [11]</td>
<td></td>
</tr>
<tr>
<td>RCPaht A</td>
<td>No residual tumour cells and/or mucus lakes only</td>
</tr>
<tr>
<td>RCPaht B</td>
<td>Minimal residual tumour (i.e. only occasional microscopic tumour foci are identified with difficulty)</td>
</tr>
<tr>
<td>RCPaht C</td>
<td>No marked regression</td>
</tr>
<tr>
<td>CAP system [12]</td>
<td></td>
</tr>
<tr>
<td>TRG 0 (complete response)</td>
<td>No residual tumour</td>
</tr>
<tr>
<td>TRG 1 (marked response)</td>
<td>Minimal residual cancer</td>
</tr>
<tr>
<td>TRG 2 (moderate response)</td>
<td>Residual cancer outgrown by fibrosis</td>
</tr>
<tr>
<td>TRG 3 (poor or no response)</td>
<td>Minimal or no tumour kill; extensive residual cancer</td>
</tr>
<tr>
<td>Modified Mandard three-point TRG system by Ryan et al. [17]</td>
<td></td>
</tr>
<tr>
<td>TRG 1</td>
<td>No cancer cells, or single cancer cells, or small group of cancer cells</td>
</tr>
<tr>
<td>TRG 2</td>
<td>Residual cancer outgrown by fibrosis</td>
</tr>
<tr>
<td>TRG 3</td>
<td>Fibrosis outgrown by cancer, or no fibrosis with extensive residual cancer</td>
</tr>
<tr>
<td>Modified Mandard four-point TRGN by Dhadda et al. [8]</td>
<td></td>
</tr>
<tr>
<td>TRGN 1</td>
<td>(Complete regression) with absence of residual cancer and fibrosis extending through the wall</td>
</tr>
<tr>
<td>TRGN 2</td>
<td>Presence of rare residual cancer cells scattered through the fibrosis</td>
</tr>
<tr>
<td>TRGN 3</td>
<td>An increased number of residual cancer cells, but fibrosis is still predominant</td>
</tr>
<tr>
<td>TRGN 4</td>
<td>Macroscopic tumour; absence of regressive; any node positive within the irradiated volume</td>
</tr>
</tbody>
</table>

Beaumont Hospital, Dublin, Ireland
- N=153 +neoadjuvant chemoXRT +adjuvant chemo
- T3/T4 +LN (locally advanced)
- Evaluated all TRG systems
- By multivariate analysis: ypN and margin not TRG

ypN and margin
University of Alexandria, Egypt
- N=121 patients + neoadjuvant chemoXRT + adjuvant chemo
- Median follow-up: at least 5 years
- +margin: tumor extension (continuous and discontinuous) <2mm from ink
- Mesorectal resection status NOT a prognostic factor for recurrence
RECTAL CARCINOMA

Sungkyunkwan University School of Medicine, Seoul, Korea
  • N=181 + neoadjuvant chemoXRT

Circumferential margin <1mm
RECTAL CARCINOMA

CAO/ARO/AIO-94 trial (multicenter randomized phase III study)
- N=124 + neoadjuvant chemoXRT
- Median follow-up: at least 5 years
- ypT3a: ≤5mm, ypT3b: >5mm
- ypT3b: HR 2.46, 95%CI 1.2-5.0, P=0.014
disease-specific survival

 ypT3a versus ypT3b
PATHOLOGIC FACTORS PROGNOSTIC OF SURVIVAL

Esophageal adenocarcinoma

- ypTNM (AJCC 6th) – conflicting studies
- LN and distant metastasis
- Tumor downstaging
- NE differentiation
PATHOLOGIC FACTORS PROGNOSTIC OF SURVIVAL

Gastric carcinoma

- R0 resection
- Pathologic response
  - Complete and <10% residual tumor
- ypTNM (AJCC 6th)
- LN status (UICC 2002)
PATHOLOGIC FACTORS PROGNOSTIC OF SURVIVAL

Pancreatic ductal carcinoma

- ypTNM (AJCC 7th)
- LN status
  - 0 vs 1-3 +LN vs >3 +LN
- +tumor in resected vein
- +invasion into muscular vessel
- Pathologic response
  - <5% vs ≥5% residual tumor
PATHOLOGIC FACTORS PROGNOSTIC OF SURVIVAL

Rectal carcinoma

- Tumor regression grade – conflicting studies
- LN status
- R0 resection
  - 1 mm vs 2 mm
- ypT3a vs ypT3b