Getting genetics into the clinic
Can we stage Oesophageal Adenocarcinomas better?

Christopher Peters
SpR in Upper GI Surgery
Chelsea and Westminster Hospital
London
'Quiet epidemic' of male cancer in UK

By Helen Briggs
BBC News

Action is needed to fight a “quiet epidemic” of oesophageal cancer, which is on the rise in the UK, particularly among men, cancer experts say.

Men are almost three times more likely than women to get the cancer - one of the biggest gender divides in cancer rates, according to new figures.

Early diagnosis is the key to saving lives, says a Cancer Research UK team.

Scientists are working on ways to detect symptoms earlier and to decipher the genetic code of the cancer.

Poor outcomes

Oesophageal cancer - cancer of the gullet or food pipe - is the ninth most common cancer in the UK.
Predicting Outcome

- GOJ Adenocarcinomas staged according to TNM 7
- Most patients present with T3N+ve Disease
  - Median survival = 15 months
  - Range 0 months >8 years
- Even in T1N-ve Disease “Early Disease”
  - Median survival = >5 years
  - Range 0 months >10 years

Molecular features are not currently used in staging

Peters et al, BJS, 2009
Molecular Staging

Validation and Clinical Utility of a 70-Gene Prognostic Signature for Women With Node-Negative Breast Cancer

Marc Buyse, Sherene Loi, Laura van’t Veer, Giuseppe Viale, Mauro Delorenzi, Annuska M. Glas, Mahasti Saghatelian d’Assignies, Jonas Bergh, Rosette Lidereau, Paul Ellis, Adrian Harris, Jan Bogaerts, Patrick Therasse, Arno Floore, Mohamed Amal, Fatima Cardoso, Martin On behalf of the TRAN

Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial

Lancet Oncol 2010; 11: 55-65

Kathy S Albain, William E Barlow, Steven Shak, Gabriel N Hortobagyi, Robert B Livingston, J-Tien Yeh, Peter Ravdin, Roberto Bugarini, Frederick I Baehner, Nancy E Davidson, George W Sledge, Eric P Winer, Clifford Hudis, James N Ingle, Edith A Perez, Kathleen I Pritchard, Lois Shepherd, Julie R Gralow, Carl Yoshizawa, D Craig Allred, C Kent Osborne, Daniel F Hayes, for The Breast Cancer Intergroup of North America

Three-Gene Expression Signature Predicts Survival in Early-Stage Squamous Cell Carcinoma of the Lung

Marcin Skrzypski,¹ Ewa Jassem,¹ Miquel Taron,² Jose Javier Sanchez,³ Pedro Mendez,² Witold Rzyman,¹ Grazyna Gulida,¹ Dan Raz,⁵ David Jablons,⁵ Mariano Provencios⁴ Bartomeu Massuti,⁶ Imane Chaib,² Laia Perez-Roca,² Jacek Jassem,¹ and Rafael Rosell²

Clin Cancer Res 2008;14(15) August 1, 2008 4794

MRC | Medical Research Council
Sequence analysis of mutations and translocations across breast cancer subtypes

What are we waiting for?

USA FDA 5 Steps of Biomarker Validation

- Phase I: Preclinical Exploration
- Phase II: Clinical assay and validation
- Phase III: Retrospective longitudinal validation
- Phase IV: Prospective validation
- Phase V: Demonstration of improved outcomes

Sensitive
Specific
Cost effective

Fast
Robust
Better than existing

Where are we so far?
What are we waiting for?

USA FDA 5 Steps of Biomarker Validation

- Phase I: Preclinical Exploration
- Phase II: Clinical assay and validation
- Phase III: Retrospective longitudinal validation
- Phase IV: Prospective validation
- Phase V: Demonstration of improved outcomes

Most GOJ signatures are not even retrospectively validated in any cancer. To be clinically useful, we need to develop ways to combine Clinical and Molecular staging.
What do we need?

- Tumour Diagnosed
- Clinical staging
- Molecular staging
- Improved prediction of outcome
What do we need?

- Tumor Diagnosed
- Clinical staging
- Molecular staging
- Improved prediction of outcome
Molecular Staging

Genome

Transcriptional Regulation

Gene Expression

Protein Expression
Molecular Staging

Genome
Copy Number Changes

Assessed copy number changes in 33 adenocarcinomas

\[ \leq 12 \text{ Aberrations} \]

\[ > 12 \text{ Aberrations} \]

No validation as yet

Pasello et al, Mod Pathology, 2009
Copy Number Changes

Identified copy number changes in 56 adenocarcinomas using array CGH and expression data

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Prognostic in external validation cohort (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 Gene</td>
<td></td>
</tr>
<tr>
<td>2 Genes</td>
<td></td>
</tr>
<tr>
<td>3-4 Genes</td>
<td></td>
</tr>
</tbody>
</table>

Goh et al et al, Gut, 2012
Genome sequencing

Exome sequencing of 149 tumour-normal matched pairs with whole genome sequencing of 16 of these

Determined GOJ tumours have a high mutation rate

26 Significantly mutated genes identified

Dulak et al et al, Nature Genetics, 2013
Molecular Staging

Transcriptional Regulation
Methylation Changes

Assessed methylation status in 41 adenocarcinomas

≤ 50 Genes Methylated

>50 Genes Methylated

p=0.04

No validation as yet

Brock et al, Clinical Cancer Research, 2009
Molecular Staging

Gene Expression
Gene Expression

Assessed E2F-1 expression in 35 adenocarcinomas

No validation as yet

Gene Expression

Assessed Met expression in 145 adenocarcinomas

No further validation as yet

Tuynman et al et al, British Journal of Cancer, 2008
Gene Expression

Expression profiled 13 patients (mixed SCC and Adeno)

113 genes correlated with response

12 genes externally validated with qPCR

8 successfully

n=28

Molecular Staging

Protein Expression
Plasma protein

Looked at plasma protein peaks in 24 adenocarcinomas

4 peaks associated with outcome

No validation as yet

Kelly et al, British Journal of Cancer, 2012
Molecular Staging

Gene Expression
A 4-Gene Signature Predicts Survival of Patients With Resected Adenocarcinoma of the Esophagus, Junction, and Gastric Cardia

CHRISTOPHER J. PETERS,* JONATHAN R. E. REES,‡ RICHARD H. HARDWICK,§ JAMES S. HARDWICK,‖ SARAH L. VOWLER,‖ CHIN-ANN J. ONG,* CHUNSHENG ZHANG,‖ VICKI SAVE,# MARIA O’DONOVAN,** DORIS RASSL,‡‡ DEREK ALDERSON,§§ CARLOS CALDAS,‖‖ and REBECCA C. FITZGERALD,* on behalf of the Oesophageal Cancer Clinical and Molecular Stratification Study Group

Peters, et al, Gastroenterology 2010
Methodology - Overview

1. Expression profiling 75 tumors at RNA level
2. Generation of a Molecular Prognostic Signature
3. Internal validation at the Protein level
4. External validation in 371 independent tumors
Methodology - Overview

1. Expression profiling 75 tumors at RNA level
2. Generation of a Molecular Prognostic Signature
3. Internal validation at the Protein level
4. External validation in 371 independent tumors
Generation of Molecular Prognostic Signature

Survival

Number of Involved lymph nodes

Low Expression  High Expression
Generation of Molecular Prognostic Signature

Expression profiled 75 Oesophageal and GOJ adenocarcinomas

- 119 Genes predictive of survival
- 270 Genes predictive of number of involved LNs

Lists ranked by a number of Statistical, Biological and Pragmatic criteria

Short list of 10 targets
Methodology - Overview

- Expression profiling 75 tumors at RNA level
- Generation of a Molecular Prognostic Signature
- Internal validation at the Protein level
- External validation in 371 independent tumors
Results- Internal validation

- **SIRT2**  $p=0.046$
  - Not Dysregulated (n=23)
  - Dysregulated (n=21)

- **PAPSS2**  $p=0.001$
  - Not Dysregulated (n=23)
  - Dysregulated (n=21)

- **TRIM44**  $p=0.063$
  - Not Dysregulated (n=15)
  - Dysregulated (n=23)

- **DCK**  $p=0.035$
  - Not Dysregulated (n=22)
  - Dysregulated (n=15)
Methodology- Overview

- Expression profiling 75 tumors at RNA level
- Generation of a Molecular Prognostic Signature
- Internal validation at the Protein level
- External validation in 371 independent tumors
External validation - Four Gene Signature

p = 0.001

0 / 4 Genes Dysregulated (n=20)

1-2 / 4 Genes Dysregulated (n=259)

3-4 / 4 Genes Dysregulated (n=58)

Good prognosis
5 year Survival = 58%

Poor prognosis
5 year Survival = 26%

Very poor prognosis
5 year Survival = 14%
Multivariate Analysis - Four Gene Signature

Entered into COX Model
- T-stage
- N-stage
- M-stage
- Differentiation
- Neurovascular Invasion
- Resection margin

Remain in Model
- T-stage
- N-stage

4 gene prognostic signature

4 gene prognostic signature
Four Gene Signature

DCK
PAPSS2
SIRT2
TRIM44
Four Gene Signature

- **DCK**
  - Involved in the phosphorylation of several deoxyribonucleosides and their nucleoside analogues
  - Deficiency is associated with resistance to chemotherapeutic agents in pancreatic cancer

  \[ \hat{X} = \text{Poor Prognosis} \]

- **PAPSS2**
- **SIRT2**
- **TRIM44**
Four Gene Signature

- **DCK**
  - Bifunctional enzyme with both ATP sulphurylase and APS kinase activity

- **PAPSS2**
  - Discovered by comparing malignant and non-malignant colorectal cell lines
  - Poor Prognosis

- **SIRT2**
  - Is commonly deleted or inactivated in prostate cancer cell lines and xenografts

- **TRIM44**
Four Gene Signature

DCK

• SIRT2 has a Mitotic Checkpoint Function

PAPSS2

• Promotes cell death when cells are under stress

SIRT2

• Downregulation confers resistance to microtubule inhibitors

TRIM44

• Drugs targeting SIRT2 are under development

↓ = Poor Prognosis
Four Gene Signature

- DCK
- PAPSS2
- SIRT2
- TRIM44

- Amplified in Head and Neck Squamous Cell Cancers
- TRIM family involved in ubiquitination pathway
- Other family members linked to prognosis in gastric cancer and breast cancer

\[ \hat{y} = \text{Poor Prognosis} \]
What do we need?

- Tumour Diagnosed
- Clinical staging
- Molecular staging
- Improved prediction of outcome
What do we need?

- Tumour Diagnosed
- Clinical staging
- Molecular staging
- Improved prediction of outcome
What do we need?

- Tumour Diagnosed
- Clinical staging
- Molecular staging
- Prognostic Index

Improved prediction of outcome
## The OCCAMS Score

Oesophageal Cancer Clinical and Molecular Stratification

### Age

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prognostic Index Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.3</td>
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### Differentiation

<table>
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<tr>
<th>Feature</th>
<th>Prognostic Index Score</th>
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<tbody>
<tr>
<td>Well differentiated</td>
<td>0</td>
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<tr>
<td>Moderately differentiated</td>
<td>0</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>3</td>
</tr>
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</table>

### T-stage

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prognostic Index Score</th>
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<tbody>
<tr>
<td>T1</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>5</td>
</tr>
<tr>
<td>T3</td>
<td>6</td>
</tr>
<tr>
<td>T4</td>
<td>20</td>
</tr>
</tbody>
</table>

### N-stage

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prognostic Index Score</th>
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<tbody>
<tr>
<td>N0</td>
<td>0</td>
</tr>
<tr>
<td>N1</td>
<td>9</td>
</tr>
<tr>
<td>N2</td>
<td>16</td>
</tr>
</tbody>
</table>

### LN Above and below the diaphragm

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prognostic Index Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four Gene Molecular prognostic signature</td>
<td>0</td>
</tr>
<tr>
<td>1-2/4 genes dysregulated</td>
<td>11</td>
</tr>
<tr>
<td>3-4/4 genes dysregulated</td>
<td>14</td>
</tr>
</tbody>
</table>
### The OCCAMS Score

**Oesophageal Cancer Clinical and Molecular Stratification**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prognostic Index Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Moderate</td>
</tr>
<tr>
<td>T-stage</td>
<td>T2</td>
</tr>
<tr>
<td>Revised N-stage</td>
<td>N0</td>
</tr>
<tr>
<td>4 Gene Signature</td>
<td>0/4 Genes Dysregulated</td>
</tr>
</tbody>
</table>

#### Prognostic Index (PI)

- **Prognosis Group:** Good

#### Chance of Survival

- **1 Year:** 97%
- **2 Years:** 94%
- **3 Years:** 91%
- **4 Years:** 88%
- **5 Years:** 86%
# The OCCAMS Score

Oesophageal Cancer Clinical and Molecular Stratification

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prognostic Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Poor</td>
</tr>
<tr>
<td>T-stage</td>
<td>T3</td>
</tr>
<tr>
<td>Revised N-stage</td>
<td>N2</td>
</tr>
<tr>
<td>4 Gene Signature</td>
<td>3-4/4 Genes Dysregulated</td>
</tr>
</tbody>
</table>

**Prognostic Index (PI)**

<table>
<thead>
<tr>
<th>Prognosis Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good = 0.35</td>
</tr>
<tr>
<td>Moderate = 36-42</td>
</tr>
<tr>
<td>Poor = 43-54</td>
</tr>
<tr>
<td>Very Poor = 55 or &gt;</td>
</tr>
</tbody>
</table>

**Prognosis Group**

<table>
<thead>
<tr>
<th>Chance of Survival</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td>43%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Years</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Years</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Years</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Years</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The **OCCAMS** Score

**Oesophageal Cancer Clinical and Molecular Stratification**

- **Good prognosis**
  - 5 year Survival = 90%

- **Moderate prognosis**
  - 5 year Survival = 52%

- **Poor prognosis**
  - 5 year Survival = 20%

- **Very poor prognosis**
  - 5 year Survival = 0%

\[ p < 0.001 \]
The OCCAMS Score

Oesophageal Cancer Clinical and Molecular Stratification

Survival (%)

Time (years)

- Good Prognosis predicted survival (n=29)
- Good Prognosis observed survival (n=29)
- Moderate Prognosis predicted survival (n=37)
- Moderate Prognosis observed survival (n=37)
- Poor Prognosis predicted survival (n=83)
- Poor Prognosis observed survival (n=83)
- Very poor Prognosis predicted survival (n=32)
- Very poor Prognosis observed survival (n=32)
Prospective Multicentre Trial of a revised clinical and molecular staging system for Esophageal and Junctional Adenocarcinoma

The OCCAMS Study
Oesophageal Cancer Clinical and Molecular Stratification

Original article

Generation and validation of a revised classification for oesophageal and junctional adenocarcinoma

C. J. Peters1,2, R. H. Hardwick3, S. L. Vowler3 and R. C. Fitzgerald4, on behalf of the Oesophageal Cancer Clinical and Molecular Stratification Study Group

1Medical Research Council (MRC) Cancer Cell Unit, Hutchison/MRC Research Centre, Addenbrooke’s Hospital, Cambridge; 2Research and Development, Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, and 3Department of Gastroenterology, Addenbrooke’s Hospital, Cambridge, UK.
Correspondence: Dr R. C. Fitzgerald, MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Hills Road, Cambridge CB2 0XY, UK (e-mail: rcf@hutch.cancerresearchuk.org)

Background: Oesophageal adenocarcinoma is the commonest oesophageal malignancy in the West, but is staged using a system designed for squamous cell carcinoma. The aim was to develop and validate a staging system for oesophageal and junctional adenocarcinoma.

Methods: Patients with oesophageal adenocarcinoma (Siewert types I and II) undergoing oesophagectomy with curative intent were randomly assigned to generation (313 patients) and validation (131) data sets. Outcome in the generation data set was associated with histopathological features; a revised node (N) classification was derived using recursive partitioning and tested on the validation data set.

Results: A revised N classification based on number of involved lymph nodes (N0, none; N1, one to five; N2, six or more) was prognostically significant (P < 0.001). Patients with involved nodes on both sides of the diaphragm, regardless of number, had the same outcome as the N2 group. When applied to the validation data set, the revised classification (including nodal number and location) provided greater discrimination between node-positive patients than the existing system (P < 0.001). Conclusions: A revised N classification based on number and location of involved lymph nodes provides improved prognostic power and incorporates features that may be useful before surgery in clinical management decisions.

Peters et al, BJS, 2009

Peters et al, Gastro, 2010
The OCCAMS Collaboration

**Plan** Whole Genome sequence 500 GOJ Adenocarcinomas + paired normal tissue

**Aim** Understand the underlying genomic changes that drive GOJ adenocarcinoma

100 Genomes Sequenced Already
The **OCCAMS** Collaboration

- Now over 15 centres
- Scientific committee formed to approve new projects
- In addition to the ICGC & prospective trial multiple other projects planned or already underway
How might molecular staging be used?

- Tumour Diagnosed
  - Clinical staging
  - Molecular staging

- Prognostic Index
  - Improved prediction of outcome
  - Improved management decisions

- Targeted therapy +/- Monitoring treatment response

MRC | Medical Research Council
Combining Clinical and Molecular Staging

• Molecular staging has huge potential

• BUT WE NEED:
  • More validation of existing signatures including prospectively
  • To combine the clinical and molecular staging in a way that is useful in the real world

We believe a Prognostic Index is one way to do this
For more info- chris.peters@doctors.org.uk

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Nick Shannon
Jonathan Rees
Johnny Ong

**Birmingham**
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Olga Tucker
Jane Darton
Richard Steyn

**Bristol**
Prof Jane Blazeby

**Cambridge**
Richard Hardwick
Peter Safranek
Nicholas Carroll
Maria O'Donovan
Doris Rasl
Carlos Caldas
Will Howat

**Oxford**
Nicholas Maynard
Nazreen Imrit
Chandima De Cates

**Edinburgh**
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**Merck**
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Chunsheng Zhang
Kyle Serikawa
Hongyue Dai
Mark Ferguson
George Tokiwa
Mollie McWhorter
Leslie Carlini

**Romford**
David Khoo
Ibtisam Saeed
Jin Tan
Ranjana Dey

**Gloucester**
Prof Hugh Barr
Prof Neil Shepherd
Simon Dwerryhouse

**Glasgow**
James Going
Robert Stuart

**Cardiff**
Geoffrey Clark

**Exeter**
Richard Berrisford
Saj Wajed
Patrick Sarsfield
Ian Chandler

**OCCAMS**
Oesophageal Cancer Clinical and Molecular Stratification

"All other things being equal, the simplest solution is the best."

Occam’s razor
14th Century

**MRC**
Medical Research Council

**MERCK**

Under Collaborative Research Agreement

**ECMC**
National Institute for Health Research
Biomedical Research Centre
Effect of Chemotherapy
Four Gene Signature

Chemo Naive

- 0 / 4 Genes Dysregulated (n=8)
- 1-2 / 4 Genes Dysregulated (n=101)
- 3-4 / 4 Genes Dysregulated (n=28)

p=0.038

Chemotherapy

- 0 / 4 Genes Dysregulated (n=11)
- 1-2 / 4 Genes Dysregulated (n=98)
- 3-4 / 4 Genes Dysregulated (n=16)

p=0.025
# Methodology

## Profiled Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>62</td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
<td>37</td>
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<tr>
<td><strong>Siewert Classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I / Esophageal</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>Type II / Junctional</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Type III / Gastric</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
<td>17</td>
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<td><strong>Chemotherapy</strong></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>71</td>
<td>93</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>5</td>
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<tr>
<td><strong>Median follow up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>20 months</td>
<td>Range 0.5 - 137</td>
</tr>
<tr>
<td>Survivors</td>
<td>89 months</td>
<td>Range 66 -137</td>
</tr>
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</table>
## Methodology

### External Validation Demographics

<table>
<thead>
<tr>
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<th>Number</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
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<td></td>
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<tr>
<td>Male</td>
<td>295</td>
<td>80</td>
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<tr>
<td>Female</td>
<td>76</td>
<td>20</td>
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<tr>
<td><strong>Siewert Classification</strong></td>
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<tr>
<td>Type I / Esophageal</td>
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<td>70</td>
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<td>Type II / Junctional</td>
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<td>Range 0.5 - 193</td>
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<tr>
<td>Survivors</td>
<td>57 months</td>
<td>Range 12 - 137</td>
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