Early Detection and Treatment of ESCC
Overview

Sandy Dawsey
NCI
ESCC Survival

5-year survival (US) 19%
5-year survival (Iran) 3%

> 90% 5-year survival < 10%

- Late Sx → late Dx → Poor survival
- Need early detection and treatment
- Need to screen at-risk adults in HR pops
Components of a Successful Early Detection and Treatment Program

<table>
<thead>
<tr>
<th>ID of precursor lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary screen</td>
</tr>
<tr>
<td>Endoscopic localization</td>
</tr>
<tr>
<td>Staging</td>
</tr>
<tr>
<td>Therapy</td>
</tr>
</tbody>
</table>
### Identification of ESCC Precursor Lesions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cumulative Incidence (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.5 yrs</td>
</tr>
<tr>
<td>Normal</td>
<td>2% (1.0)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>0% (---)</td>
</tr>
<tr>
<td>Mild Dysplasia</td>
<td>5% (2.2)</td>
</tr>
<tr>
<td>Moderate Dysplasia</td>
<td>27% (15.8)</td>
</tr>
<tr>
<td>Severe Dysplasia</td>
<td>67% (67.6)</td>
</tr>
</tbody>
</table>

- Moderate and severe dysplasia are the clinically important precursor lesions

Dawsey et al Cancer 1994; Wang et al Gut 2010
Endoscopic Localization of Dysplasia
Mucosal staining with Lugol’s iodine solution

- Iodine reversibly stains glycogen → normal epithelium is brown, dysplasia is unstained

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity of USLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>---</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>---</td>
</tr>
<tr>
<td>Mild Dysplasia</td>
<td>63%</td>
</tr>
<tr>
<td>Moderate Dysplasia</td>
<td>93%</td>
</tr>
<tr>
<td>Severe Dysplasia</td>
<td>96%</td>
</tr>
</tbody>
</table>

Dawsey et al Cancer 1998
Staging

PARIS Classification

Basic Pattern

- Protruding
  - Pedunculated
  - Sessile
- Slightly protruding
- Nonprotruding and Nonexcavated
  - Completely flat
  - Slightly depressed
- Excavated

Mixed Pattern

- 0-Ip
- 0-Ia
- 0-Ic
- 0-IIa
- 0-IIb
- 0-IIc
- 0-III
- 0-Ic + IIa
- 0-Ic + IIc
- 0-Ia + IIa
- 0-Ia + IIc
- 0-IIa + IIc
- 0-IIa + III
- 0-Ic + III
- 0-III + IIc

<10% 40%
Endoscopic Therapy for Early Esophageal Squamous Neoplasia
(Moderate Dysplasia, Severe Dysplasia, T1m2 ESCC)

• Excisional methods (EMR, MBM, ESD)

• Ablative methods (APC, RFA)

Pictures courtesy of Jacques Bergman
The National Esophageal Cancer Early Detection and Treatment Program of China

- Lugol’s chromoendoscopy, biopsy USLs > 5mm
- Endoscopic Therapy of flat HGD
- 10-year F/U → 33% reduction in ESCC mortality

- >100 Field Sites, each screening ~ 2,000 asx 40-69yo adults/yr
- > 200,000 screened each year
- > 40,000,000 adults of this age live in the high risk areas

- Need an accurate non-endoscopic primary screen that can screen millions and triage those at highest risk to endoscopy
## Esophageal Cancer Incidence Rates in Population-Based Cancer Registries

<table>
<thead>
<tr>
<th>Location</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cixian, China</td>
<td>193</td>
<td>109</td>
</tr>
<tr>
<td>Yanting, China</td>
<td>101</td>
<td>68</td>
</tr>
<tr>
<td>Golestan, Iran</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Nairobi, Kenya</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Blantyre, Malawi</td>
<td>38</td>
<td>23</td>
</tr>
<tr>
<td>Eastern Cape Province, RSA</td>
<td>32</td>
<td>20</td>
</tr>
</tbody>
</table>

Cancer Incidence in Five Continents, Vol X, IARC

- Endoscopic screening may be cost-effective in Cixian or Yanting, but it will never be cost-effective in most other HR populations.
- We need a less expensive non-endoscopic primary screening test that can accurately triage patients to or away from endoscopy.
Esophageal Balloon Cytology
## Esophageal Balloon Cytology

### Cytology - Histology Comparisons

<table>
<thead>
<tr>
<th></th>
<th>CSS1</th>
<th>CSS1</th>
<th>CSS2</th>
<th>CSS2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>47%</td>
<td>24%</td>
<td>46%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>81%</td>
<td>92%</td>
<td>84%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Roth et al, Cancer 1997; Pan et al, Acta Cytol 2008

- Current EBC methods are insufficient for primary screening
- Can molecular markers help?
  - An adjunct to cytology
  - Separate from cytology
  - Screening for dysplastic cells
  - Screening for a field effect
Potential Molecular Markers for ESCC Screening

Cytosponge – TFF3 Staining in BE

Methylation Profiling

Copy Number Variation
Using Methylated DNA Markers for Detection of BE

Phase 1
• Identify discriminant methylated DNA markers (MDMs) for BE by whole-methylome discovery and subsequent biologic validation of biopsies of squamous epi, BE, and cardia

Phase 2
• Assess accuracy of candidate MDMs for BE in endoscopic brushings from whole esophagus and cardia

Phase 3
• Pilot test best candidate MDMs on cytology specimens from a sponge capsule device

Iyer, Ahlquist et al, DDW 2016
Phase 3: Summary Results

Top 2 markers
100% Sens
100% Spec

Iyer, Ahlquist et al. DDW 2016
Esophageal Squamous Cell Carcinoma
How Can We Improve the Current Situation?

Game Changers
• Find an infectious cause/co-factor
• Develop a clinically useful non-endoscopic primary screening test for HGD

Significant Improvements
• Etiologic studies in Africa
• Selenium added to fertilizer in low-Se HR areas
• Chimneys on cookstoves in HR areas
• Making stents available for palliative care