SUPERFICIAL ESOPHAGEAL SCC

Title: How to treat early esophageal SCC after dissection?
Endoscopic treatment

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Université Catholique de Louvain
Country: BELGIUM
Introduction

- 8th cause of death from cancer
- SCC
  - 4-16 cases/100,000 in Europe
  - 50% of esophageal cancers in Europe
  - 90% of esophageal cancers in Japan

Messmann H, Best Pract Res Clin Gastroenterol 2001
Hhushi K, Gastrointest Cancer Res 2009
Squamous cell cancer

- SCC: >70% dg stage III-IV, 5y survival<5%
- Esophagectomy
  - Mortality 3%, morbidity 40%

- Early/superficial: T1a and b
- Aim of endotherapy = cure
  - R0 and risk of LNM<3%

Characteristics of early SCC

- Frequent multiple lesions
- Poor delineation
- Association with ENT lesions
- More rapid lymph-node involvement
- Frequent metachronous lesions

- Need for large resections
- Precise lateral resection margins
- May occur in irradiated areas
- Most accurate T-staging is required
- Subsequent resections sometimes required
SCC: Risk of lymph node metastasis

- T1a-EP (M1): 0%
- T1a-LPM (M2): 9-21%
- T1a-MM (M3): 47-55%
- SM1 (SM1)
- SM2 (SM2)
- SM3 (SM3)

Epithelium
Lamina propria mucosa
Muscularis mucosa
Muscularis propria
Indications for endoscopic treatment

• Japan Esophageal Society Guidelines
  – m1-m2= absolute indication
  – m3-sm1 (<200µm) = relative indication

• SCC-risk factors for LNM:
  – G2-3
  – L+, V+
  – Infiltrative growth

Kuwano, H. et al. Esophagus 2008:5; 61–73
Oyama T, et al. Stomach and Intestine 2002:37; 72–74
Non-invasive type (N-I type)

Invasive type (I type)

Courtesy of Dr. Ueno, Dept. of Surgery, Toranomon Hosp.
# Evaluation of risk factor for LN metastasis

**Depth of cancer: m3 & sm ≤200μm (n= 70)**

<table>
<thead>
<tr>
<th></th>
<th>pN-</th>
<th>pN+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N-I type</strong></td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td><strong>I type</strong></td>
<td>30</td>
<td>12 (28.6%)</td>
</tr>
</tbody>
</table>

\[(P=0.0019)\]

<table>
<thead>
<tr>
<th></th>
<th>pN-</th>
<th>pN+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ly-</strong></td>
<td>48</td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>ly+</strong></td>
<td>10</td>
<td>10 (50%)</td>
</tr>
</tbody>
</table>

\[(P<0.0001)\]

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Courtesy of Dr. Ueno, Dept. of Surgery, Toranomon Hosp.
Methods of endoscopic treatment

• **RESECTION**
  – EMR
  – ESD

• **ABLATION**
  – RFA (2 papers)
  – PDT (case series, combination)
  – Others

• **ASGE guidelines**
  – We suggest that EMR or ESD be used for the treatment and staging of suspected intramucosal SCC
  – We suggest that APC, heater probe, cryotherapy, or RFA not be used as monotherapy with curative intent for mucosal esophageal cancer

ASGE GIE 2013
RFA and SCC

- RFA has the potential to become an important technique for the treatment of early esophageal SCC, especially in areas where the disease is endemic.
- This technique does not require a high level of endoscopic expertise and enables treatment of widespread or mosaic-like early lesions for which endoscopic resection would likely result in complications.

RFA and SCC

- Prospective study of flat MGIN, HGIN, ESCC
- RFA was associated with a high rate of histological CRs (97% of patients)
- No neoplastic progression, and an acceptable adverse event profile

EMR vs. ESD in SCC
EMR for SCC

• Asia and Europe show similar results
  – EMR for early SCC is associated with local recurrence rates of 10% to 26%.
  – In two of the larger series, subanalysis limited to high-grade intraepithelial neoplasia and T1m2 lesions reported recurrence rates of 13% to 18%

• EMR should ONLY be performed for tumours < 2 cm that can be removed en block in a single specimen and with no risk factor

EMR for SCC: only for lesions < 20 mm

Ishihara et al. Gastrointest Endosc 2008;67:799-804
EMR for SCC: only for lesions < 20 mm
ESD for SCC: gold standard

- Lesions >2 cm
- Better R0, en bloc rates
- Better pathology specimen
- Fewer recurrences
  - Major factor for recurrence: R1 and piecemeal resection
- Safe in expert hands
  - Perforation rate 2%

Takahashi et al. Gastrointest Endosc 2010
Basic principles of ESD procedure

1. Spraying
2. Marking
3. Local injection
4. Circumferential incision
5. Hemostasis
6. Collection
7. Submucosal dissection
Cutting and dissecting knives

– Olympus knives
– Fujinon Flush knives
– ERBE Hybrid knife
– Pentax prototypes

– Types
  • Needle knife type
    – Need injection needle
  • IT knife type
    – Needs needle knife to create a hole
    – Need injection needle
  • Flushing type
    – No injection needle needed
<table>
<thead>
<tr>
<th></th>
<th>Longitudinal approach</th>
<th>Lateral approach</th>
<th>Speed</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very Good</td>
<td>Not Good</td>
<td>Very Good</td>
<td>Effective in longitudinal incision</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Good</td>
<td>Not Good</td>
<td>Tends to cut blind</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Safe but takes time, as it hooks and cuts the fiber in the submucosal layer little by little</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Proper cutting speed in all directions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Requires less skill</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>There’s no need to rotate the knife and cutting can easily be performed in the direction you want</td>
</tr>
</tbody>
</table>
Other devices

- **Cap “transparent disposable attachment”**
  - Better viewing
  - Keep appropriate distance to working field
  - Lift the mucosa
  - Press when bleed occurs

- **Solutions**
  - Saline
  - Hyaluronic acid
  - Gelatin
  - Artificial tears (hydroxyl propyl methyl cellulose)
  - “Japanese mixture” Glyceol consisting of 10% glycerol and 5% fructose in a normal saline solution (Chugai Pharmaceutical Co., Tokyo, Japan)

- **Lifting devices**
  - Endolifter
  - Band-clip
  - Thread-clip traction

- **CO²**
- **General anesthesia/intubation**
# Bleeding

<table>
<thead>
<tr>
<th>Device</th>
<th>Usage/Caution</th>
<th>HQ machine setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT Knife</td>
<td>For venous bleeding</td>
<td>Forced, 50W (ICC200)</td>
</tr>
<tr>
<td>Flex/Dual Knife</td>
<td>Venous bleeding: Simply press the coagulation pedal</td>
<td>Forced, 40W (ICC200)</td>
</tr>
<tr>
<td>Triangle Knife</td>
<td>If gushing bleeding occurs, bring the triangular tip in contact with the bleeding point and start coagulation for hemostasis</td>
<td>Forced, 60W (ICC200) Or Coag. (Forced), 80W, Effect 2 (PSD-60)</td>
</tr>
<tr>
<td>Hot Biopsy forceps</td>
<td>Venous bleeding: Possible to confirm hemostasis by grasping. If hemostasis is performed without confirmation, carbonization will make incision difficult.</td>
<td>Forced, 80W (ICC200) Or Soft Coag., 80W, Effect 6-8 (PSD-60)</td>
</tr>
<tr>
<td>Hemostatic forceps</td>
<td>For venous and arterial bleeding:</td>
<td>Soft Coag., 50~60W (ICC200)</td>
</tr>
</tbody>
</table>

Other measures: Clipping, APC, and HSE injection
Other settings: spray coagulation, swift coagulation
Perforations

• Clips
• Endoloops
• Stents
• Suturing
• New devices
Increase speed

• Flush or jet knives

• Thread-clip assisted
  – facilitates dissection of superficial lesions in esophageal locations
  – better view of the submucosal layer
  – lesser need for repeated submucosal fluid injection
### TABLE 2. Comparison of clinical outcomes between the EMR and ESD group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EMR group n = 184</th>
<th>ESD group n = 116</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up period, months (range)</td>
<td>82.9 (8-174)</td>
<td>35.8 (8-63)</td>
<td>.001</td>
</tr>
<tr>
<td>Mean resected specimen, mm ± SD (range)</td>
<td>25 ± 6 (12-43)</td>
<td>41 ± 15 (17-100)</td>
<td>.0002</td>
</tr>
<tr>
<td>Follow-up rate (%)*</td>
<td>184/186 (98.9)</td>
<td>116/116 (100)</td>
<td>.99</td>
</tr>
<tr>
<td>Mucosal defect over three-fourths of the whole circumference</td>
<td>10(5.4)</td>
<td>26(22.0)</td>
<td>.0001</td>
</tr>
<tr>
<td>Operation time, minutes ± SD (range)</td>
<td>44.4 ± 32.6 (11-258)</td>
<td>73.9 ± 45.8 (21-307)</td>
<td>.0007</td>
</tr>
<tr>
<td>Perforation, no. (%)</td>
<td>3 (1.6)</td>
<td>3 (2.6)</td>
<td>.68</td>
</tr>
<tr>
<td>Mediastinal emphysema, no. (%)</td>
<td>3 (1.6)</td>
<td>5 (4.3)</td>
<td>.27</td>
</tr>
<tr>
<td>Pneumonia, no. (%)</td>
<td>0 (0)</td>
<td>3 (2.6)</td>
<td>.06</td>
</tr>
<tr>
<td>Stenosis, no. (%)</td>
<td>17 (9.2)</td>
<td>20 (17.2)</td>
<td>.07</td>
</tr>
<tr>
<td>Pathological margins free rate (%)</td>
<td>144 (78.3)</td>
<td>113 (97.4)</td>
<td>.0002</td>
</tr>
<tr>
<td>Curability+ A/B/C (number)</td>
<td>144/11/29</td>
<td>115/0/1</td>
<td>.0005</td>
</tr>
<tr>
<td>En bloc resection rate, no. (%)</td>
<td>98 (53.3)</td>
<td>116 (100)</td>
<td>.0009</td>
</tr>
<tr>
<td>Local recurrence rate, no. (%)</td>
<td>18 (9.8)</td>
<td>1 (0.9)</td>
<td>.0065</td>
</tr>
<tr>
<td>Nodal metastasis rate, no. (%)</td>
<td>4 (2.2)</td>
<td>0 (0)</td>
<td>.161</td>
</tr>
<tr>
<td>Distant metastasis rate, no. (%)</td>
<td>5 (2.7)</td>
<td>0 (0)</td>
<td>.160</td>
</tr>
</tbody>
</table>

*Takahashi, Gastrointest Endosc 2010*
ESD vs. EMR for SCC

Takahashi, Gastrointest Endosc 2010
ESD for SCC in Europe

ORIGINAL ARTICLE: Clinical Endoscopy

Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series

Alessandro Repici, MD, Cesare Hassan, MD, Alessandra Carlino, MD, Nico Pagano, MD, Angelo Zullo, MD, Giacomo Rando, MD, Giuseppe Strangio, MD, Fabio Romeo, MD, Rinaldo Nicita, MD, Riccardo Rosati, MD, Alberto Malesci, MD

Milan and Rome, Italy

Capsule Summary

What is already known on this topic

- Endoscopic mucosal dissection (ESD) facilitates en bloc resection, regardless of tumor size.

What this study adds to our knowledge

- In a single-center, observational study, ESD achieved en bloc resection with resection-free margins in 18 of 20 patients with superficial esophageal squamous cell neoplasia.
- No local or distant recurrence occurred at a median follow-up of 18 months.

Figure 1. A, 3-cm superficial squamous cell carcinoma presenting as irregular area of the thoracic esophagus under conventional white light. B, The artificial slit after resection has been completed and C, the resected specimen with the lesion in en bloc fashion is shown.
## ESD for SCC: UCL St-Luc experience

<table>
<thead>
<tr>
<th></th>
<th>EMRC (n=27)</th>
<th>ESD (n=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of lesions</strong></td>
<td>30</td>
<td>30</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>60 [49-79]</td>
<td>60 [40-83]</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (63.0%)</td>
<td>22 (81.5%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (37.0%)</td>
<td>5 (18.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Paris classification type</strong></td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>0-IIa</td>
<td>14 (46.7%)</td>
<td>12 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>0-IIb</td>
<td>11 (36.7%)</td>
<td>13 (43.3%)</td>
<td></td>
</tr>
<tr>
<td>0-IIc</td>
<td>5 (16.7%)</td>
<td>5 (16.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pre treatment histology</strong></td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>HGIN</td>
<td>5 (16.7%)</td>
<td>8 (26.7%)</td>
<td></td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>25 (83.4%)</td>
<td>22 (73.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Median tumor size (mm)</strong></td>
<td>15.0 [5.0-50.0]</td>
<td>30.0 [8.0-90.0]</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Circumference</strong></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;1/2</td>
<td>21 (70.0%)</td>
<td>11 (36.7%)</td>
<td></td>
</tr>
<tr>
<td>1/2≤ &lt;3/4</td>
<td>5 (16.7%)</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>≥3/4</td>
<td>4 (13.3%)</td>
<td>12 (40.0%)</td>
<td></td>
</tr>
</tbody>
</table>
# ESD for SCC: UCL St-Luc experience

<table>
<thead>
<tr>
<th></th>
<th>EMRC (n=27)</th>
<th>ESD (n=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>En bloc resection rate</td>
<td>27%</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median number of piece</td>
<td>3.0 [1.0-12.0]</td>
<td>1.0 [1.0-1.0]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median histological surface (mm²)</td>
<td>285 [54-900]</td>
<td>775 [96-4160]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median operation time (min)</td>
<td>51 [20-85]</td>
<td>102 [17-243]</td>
<td>0.002</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stricture</td>
<td>6 (20.0%)</td>
<td>5 (16.7%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Depth of invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGD (Low grade dysplasia)</td>
<td>1 (3.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HGIN, m1, m2</td>
<td>19 (63.3%)</td>
<td>9 (30.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>m3, sm1</td>
<td>8 (26.7%)</td>
<td>19 (63.3%)</td>
<td></td>
</tr>
<tr>
<td>sm2</td>
<td>1 (3.3%)</td>
<td>2 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1 (3.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Resected margins free rate (R0)</td>
<td>50.0%</td>
<td>76.7%</td>
<td>0.03</td>
</tr>
<tr>
<td>Lymphatic or venous invasion rate</td>
<td>6.7%</td>
<td>16.7%</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>EMRC group</td>
<td>ESD group</td>
<td>( P ) value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------</td>
<td>-----------</td>
<td>---------------</td>
</tr>
<tr>
<td>Median follow-up period (months)</td>
<td>69 [5-136]</td>
<td>24 [5-51]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjuvant treatment after endoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>3 (11.1%)</td>
<td>4 (14.8%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Radiochemotherapy</td>
<td>4 (14.8%)</td>
<td>4 (14.8%)</td>
<td></td>
</tr>
<tr>
<td>Local recurrence</td>
<td>8 (26.7%)</td>
<td>1 (3.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>3 (11.1%)</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>Disease-related deaths</td>
<td>4/27 (14.8%)</td>
<td>0/27</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous, synchronous or metachronous ENT cancer</td>
<td>5/27 (18.5%)</td>
<td>10/27 (37.0%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Prognostic factors of lower DFS
Multivariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Hazard ratio</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete resection (R1)</td>
<td>80.5</td>
<td>3.0-2127.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Lesion circumference (≥3/4)</td>
<td>9.3</td>
<td>1.6-53.7</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Disease free survival

grp = EMRC
grp = ESD
ESD for SCC : UCL St-Luc experience

• What about sm1 tumours?
Esophageal lesions
(278 pts)

BAC suspect
(188 pts)

Excluded 34 pts
IM: 16, LGD: 13, T2:5

BAC T1N0M0
(154 pts)

HGD/m1-4: 136 pts
sm1: 8 pts
sm2-3: 10 pts

SCC suspect
(90 pts)

Excluded 14 pts
Other dg: 9, LGD: 2, T2:3

SCC T1N0M0
(76 pts)

HGD/m1-3: 61 pts
sm1: 13 pts
sm2-3: 2 pts

Excluded 34 pts
IM: 16, LGD: 13, T2:5

Excluded 14 pts
Other dg: 9, LGD: 2, T2:3
RESULTS - outcome SCC

<table>
<thead>
<tr>
<th>Pathology</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>size mm (IQR)</td>
<td>40 (34-52)</td>
</tr>
<tr>
<td>G1/G2/G3, n</td>
<td>5/7/1</td>
</tr>
<tr>
<td>Sm1 focal, n(%)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Ly+, n(%)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>R0, n(%)</td>
<td>8 (62)</td>
</tr>
</tbody>
</table>

Flowchart:

- Tsm: 13 pts
  - R0, G1-2, Ly0: 6 pts
    - surg 1 pt
      - alive: 2 pt
      - dead: 1 pt (all-cause)
    - no th 4
      - alive: 3 pt
    - Radio 1
      - alive: 1 pt
      - dead: 1 pt
  - R1, G3, Ly1: 7 pts
    - no th 6
      - recidive 3
        - alive: 2 pt
      - rec no 3
        - alive: 2 pt
So in SCC with sm1 invasion

– In low risk profile ER is a valid curative option
  • no recurrence after R0 ER, no disease related death

– In high risk profile
  • 3 recurrences (2 pts Ly+, 1 pt G3)
  • 1 cancer related death

– In our series, surgery plays a limited role regardless of the risk-profile; due to multiple contraindications
– Survival curves are indeed impaired by other factors, not only LNM
Conclusions

Endotherapy should be right from the start:

- Expertise in detection and precise delineation

ESD gold standard

- R0 and en block mandatory
- Better for fibrosis (post Radiotherapy)
- Circumferential resection may be needed for R0

Safe profile for ESD in expert hands

- Similar results W vs. E provided to undergo adequate training

EMR OK for small lesions (<15 mm)
No role for RFA ablation
Conclusions

Indications for endotherapy depend on:
- pre-operative staging
  . T and N stage based on HRE, EUS
  . circumferential extent
- pathology specimen staging
  . m1-m2: good indication
  . m3-sm1: relative indication
  . other factors: G, invasive pattern, L and V
  . sm1 OK if low risk or patient factors
    (practically few indications for surgery)
- patient co-morbidity (ENT cancer, previous radiotherapy, age, ...)
- local expertise