Esophageal cancer – is combination with surgery (stents) or EBRT a better solution?

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The role of esophageal brachytherapy

• The role of esophageal brachytherapy
  – Curative indications
    • locally advanced T(2)-3 tumors in combination with external beam radiotherapy
    • especially in bleeding, ulcerating, and/or obstructive tumors
The role of esophageal brachytherapy

• The role of esophageal brachytherapy (EB)
  – Curative indications
    • locally advanced T(2)-3 tumors in combination with external beam radiotherapy
    • especially in bleeding, ulcerating, and/or obstructive tumors – EB is locally very effective!

• CONS: relatively high treatment related tox
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A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report.


Treatment (n=49)

50 grays (Gy) external beam radiation (25 fractions given over 5 weeks) followed 2 weeks later by EB (either HDR 5 Gy during weeks 8, 9, and 10, for a total of 15 Gy, or LDR 20 Gy during Week 8)

Chemotherapy was given during weeks 1, 5, 8, and 11, with cisplatin 75 mg/m(2) and 5-fluorouracil 1000 mg/m(2)/24 hours in a 96-hour infusion.

Results

Survival rate at 12 months was 49% (estimated median survival of 11 mo.)

Life-threatening toxicity or treatment-related death occurred in 12 (24%) and 5 (10%) cases, respectively.

Treatment-related esophageal fistulas occurred in 6 cases (12% overall, 14% of patients starting EB) at 0.5-6.2 months from the first day of brachytherapy, leading to death in 3 cases (6%).
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Only combined modality protocols compared favorably with the previously reported results

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Predictors for better survival:
Multimodality treatment regimens (<0.0001)
Dose >50 Gy vs. <50 Gy (0.119)
EBRT + EB vs. EBRT only (0.942)


Treatment (n=103):
After 60 Gy stratified into 2 groups: external irradiation boost of 10 Gy versus HDR or LDR EB 10 Gy (2 x 5 Gy once-weekly schedule, reference dose at depth of 5 mm of the esophageal submucosa)

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  Results:
  Overall survival rate was 20.3% at 5 years
  Cause-specific survival rate was 31.8% at 5 years (27% in the external irradiation alone group and 38% in intraluminal brachytherapy combined group, p = 0.385)

  Interestingly: CSS in TU 5 cm or less tumor length 64% at 5 years in EBRT + EB versus 31.5% in EBRT alone (p = 0.025), and trend in T1-2, no difference T3-4


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  – Curative indications
  • Lessons learned
  1. Yes – very effective in terms of local control
  2. Yes – very effective in terms of controlling symptoms
  3. No – not adding benefit in survival (CSS benefit in small TUs?)
  4. However, please be careful with late toxicity
    » Especially fistula and stenosis
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  • Additional aspects – Meta-analysis (3 Y mortality)


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The role of esophageal brachytherapy

- The role of esophageal brachytherapy (EB)
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  - Additional aspects – Meta-analysis (effect of treatment on postoperative mortality)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>OR (95% CI random)</th>
<th>Weight (%)</th>
<th>OR (95% CI random)</th>
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<tbody>
<tr>
<td>Ngoprot et al.</td>
<td>8/24</td>
<td>5/38</td>
<td>21.8</td>
<td>2.03</td>
<td>[0.99, 6.95]</td>
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<tr>
<td>Aznar et al.</td>
<td>5/24</td>
<td>6/34</td>
<td>17.8</td>
<td>1.33</td>
<td>[0.25, 5.39]</td>
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<td>La Paz et al.</td>
<td>3/25</td>
<td>5/44</td>
<td>11.8</td>
<td>1.31</td>
<td>[0.55, 6.97]</td>
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<tr>
<td>Welsh et al.</td>
<td>5/51</td>
<td>2/55</td>
<td>11.6</td>
<td>2.88</td>
<td>[0.32, 15.56]</td>
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<tr>
<td>Rausert et al.</td>
<td>17/135</td>
<td>15/127</td>
<td>21.2</td>
<td>2.71</td>
<td>[1.25, 10.36]</td>
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<tr>
<td>Urbas et al.</td>
<td>1/47</td>
<td>3/50</td>
<td>3.6</td>
<td>0.52</td>
<td>[0.05, 5.95]</td>
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<tr>
<td>Total (95% CI)</td>
<td>37/338</td>
<td>22/355</td>
<td>100.0</td>
<td>2.10</td>
<td>[1.18, 3.73]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=3.25$, df=5, $p=0.66$.
Test for overall effect: $z=2.53$, $p=0.01$.


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  - Palliative indications

Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial.

(Sahlgrenska University Hospital, Göteborg, Sweden)

Treatment (n=65):

Ultraflex expandable stent or HDR endoluminal brachytherapy with 7 Gy x 3 given in 2-4 weeks

Endpoints: Clinical assessment and health-related quality of life (HRQL) were measured at inclusion and 1, 3, 6, 9 and 12 months later.
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Results (n=65):
For stent group significantly better HRQL scores for dysphagia (P < 0.05) at the 1-month follow-up, but most other HRQL scores, including functioning and symptom scales deteriorated.

Among brachytherapy-treated patients, improvement was found for the dysphagia-related scores at 3-months follow-up.

No Δ in median survival

The role of esophageal brachytherapy

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  – Palliative indications – confirmed by RCT’s

Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial.

Homs MY et al. Lancet 2004 Oct 23-29;364(9444):1497-504. (Erasmus MC/University Medical Centre Rotterdam, Netherlands)

Treatment / Results (n=209):
Stent placement (n=108) or single-dose (12 Gy) brachytherapy (n=101)
Dysphagia improved more rapidly after stent placement than after brachytherapy, but long-term relief of dysphagia was better after brachytherapy.

Stent placement had more complications (36 [33%] of 108 vs. 21 [21%] of 101; p=0.02).
Groups did not differ for persistent or recurrent dysphagia (p=0.81), or for median survival (p=0.23).
The role of esophageal brachytherapy

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  ─ Palliative indications
  • EB is very effective in improving dysphagia
  • ED effect is longer lasting
    – However, insertion of self-expandable metal stents offers a more instant relief

The role of esophageal brachytherapy

• The role of esophageal brachytherapy (EB)
  ─ Palliative indications
  • Logical question: can we combine stent insertion and single high-dose brachytherapy?
    – Aim: Both 1/ prompt effect (stent), and 2/ more long-lasting relief of dysphagia and a better health-related quality of life (HRQL) – effect of brachytherapy
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Combined stent insertion and single high-dose brachytherapy in patients with advanced esophageal cancer - results of a prospective safety study.

(Sahlgrenska University Hospital, Gothenburg, Sweden)

Treatment (n=12):
Stent insertion followed by a single dose (12 Gy) of brachytherapy

Results:
Relief of dysphagia was achieved in the majority of cases (10/11, P < 0.05), but HRQL did not improve except for dysphagia-related items.
Only minor adverse events, including chest pain, reflux, and restenosis, were reported. The median survival time after inclusion was 6.6 months.
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Combination of biodegradable stent placement and single-dose brachytherapy is associated with an unacceptably high complication rate in the treatment of dysphagia from esophageal cancer.

(University Medical Center Utrecht, the Netherlands)

Treatment (n=19):
Single-dose brachytherapy (12 Gy) on day 1 followed by biodegradable stent placement on day 2

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Results (n=19):
Positive - 1/ Dysphagia scores decreased significantly from a median of 3 (IQR 3-4) to a median of 1 (IQR 0-3) after 1 month (P < .001). + 2/ adequate luminal patency in 17 patients (89%)
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Results (n=19):
Negative - In 9 patients (47%), major intervention-related complications (severe retrosternal pain with or without vomiting [n = 6], hematemesis [n = 1], recurrent dysphagia [n = 2].

Conclusions and Acknowledgments

• Conclusions
  – Esophageal brachytherapy (EB) is very effective in terms of local tumor control
  – EB (8-10 Gy, 2 x 4-5 Gy once-weekly schedule) may be used as alternative boost procedure in experienced hands after 50 (-60) Gy EBRT
  – However, combination of higher doses (15-20 Gy?) or with chemotherapy? – maybe unsafe and toxic
  – Patient selection for ED boost remains unsolved: bleeding/ulcerating/obstructing TUs, < 5 cm length?
  – ED for palliation in dysphagia is standard treatment (long-lasting effect + more pronounced HRQoL benefit (combination with stent maybe unsafe?)
Conclusions and Acknowledgments

• Acknowledgments to the brachy team!

Brachy-Team
Physicist Herberholz
Katja Holz Dr. Hepp
Mrs. Taspinar Dr. Ammerpohl

Conclusions and Acknowledgments

• Many thanks for invitation and your attention!

Fraction dose 4 Gy in 5 mm depth esophageal appl., 30F (Ø 10 mm)