Primäre und adjuvante Strahlentherapie des Zervixkarzinoms

V. Strnad, Erlangen

- Perkutane Strahlentherapie
- Brachytherapie
- Simultane Chemotherapie

Update June 2013
Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis (Review)

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC)

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

http://www.thecochranelibrary.com
Figure 3. Subgroup analysis for FIGO stage for chemoradiotherapy versus radiotherapy trials only (Overall survival and Disease-free survival)

Survival

Hazard Ratio (Fixed)

Stage
1a-2a
2b
3-4a

Test for trend: \( \chi^2 = 5.65, p = 0.017 \)

Disease-free survival

Stage
1a-2a
2b
3-4a

Test for trend: \( \chi^2 = 3.21, p = 0.073 \)

CTRT Better

Control Better
No evidence of a difference in the size of the effect of chemoradiotherapy when trials were grouped according to the type of chemotherapy they had used (platinum-based or non-platinum-based). Similarly, for the ten trials that used cisplatin-based chemoradiotherapy (Chen 1997a; Chen 1997b; Cikaric 2005; Garipau 2004; Keys 1999; Lal 2004; Lanciano 2005a; Leborgne 1995; Onishi 2000; Pearcey 2002; Pras 1995), we found no evidence that the effect of chemoradiotherapy differed according to the cycle length or the dose intensity of cisplatin used (Table 2).

However, the power of these analyses, particularly those involving just the cisplatin-based chemoradiotherapy trials, is limited.
Summary

1. Based on the main analysis, there was clear evidence that adding chemotherapy to radiotherapy improves both OS and DFS. For the group of 13 trials in which chemoradiotherapy alone was used, there was a \textbf{6\% absolute survival benefit} and a \textbf{8\% DFS benefit at 5 years}.

2. Importantly, this meta-analysis shows that the benefit associated with chemoradiotherapy \textbf{may not depend on the use of platinum}.

3. For women who are unable to tolerate cisplatin, or more easily tolerated chemotherapy is required, \textbf{non-cisplatin based chemoradiotherapy} perhaps offers an additional option.
- Simultane Radiochemotherapie

- Brachytherapie
Zervixkarzinom - Brachytherapie

RTOG 0128

"Spin-off product"

Fig. 3. Disease-free survival for patients receiving brachytherapy versus no brachytherapy. Solid line indicates brachytherapy and dashed line, no brachytherapy.
Local recurrence rates in the individual tumour groups and the total patient population.

<table>
<thead>
<tr>
<th>Tumour group</th>
<th>Number of patients</th>
<th>Number of LR</th>
<th>% LR</th>
<th>D90 HR CTV ±SD</th>
<th>D100 HR CTV ±SD</th>
<th>% Patients with chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor&lt;5cm</td>
<td>64</td>
<td>2</td>
<td>3.1</td>
<td>89 ± 17</td>
<td>65 ± 11</td>
<td>47</td>
</tr>
<tr>
<td>Tumor&gt;5cm</td>
<td>77</td>
<td>16</td>
<td>20.8</td>
<td>83 ± 15</td>
<td>65 ± 8</td>
<td>68</td>
</tr>
</tbody>
</table>

**Local control 90-100%**

Fig. 1. Dose–response relationships (D90 in the HR CTV) for local control in the total patient population (left panel), for group 2 (large tumours, middle panel) and for group 2b (large, non-responding tumours, right panel). Particular values of the curves are presented in Table 3.
Zervixkarzinom – bildgestützte Brachytherapie
Zervixkarzinom – Brachytherapie

Applikatoren

Update
June 2013
Thus, they concluded that MRI remained the standard for CTV definition. More recently, Potter et al. [100] reported clinical outcome of MRI-guided brachytherapy combined with 3D conformal radiotherapy in locally advanced cervical cancer. They showed an excellent overall local control of 95% (98% and 92% for tumors 2–5 cm and >5 cm, respectively) with low late toxicity (only 7.7% of grade 3–4 events). They also reported a relative reduction of pelvic recurrence by 65–70% compared with historical Vienna series.
Zervixkarzinom - Brachytherapie

Zusammenfassung:

1. Strahlentherapie des Zervixkarzinoms ohne Brachytherapie ist als eine palliative Therapie zu betrachten.

2. Verzicht auf die Brachytherapie im kurativen Einsatz ist ein Kunstfehler.


- Intrakavitative & interstitielle Brachytherapie
- HR-CTV, OAR
Zervixkarzinom - Brachytherapie

„...man muss es können...!“
Statement:

1. Eine **simultane** Radiochemotherapie ist immer durchzuführen  
   *(BENEFIT 6-8%)*

   1. Cisplatin 30-40 mg/m² / weekly
   2. Wenn nicht möglich, dann ein „non-cisplatin Schema“ soll indiziert werden

   *(z.B. 5-FU/Mito C)*

   *(BENEFIT 50-70%)*
Zervixkarzinom – Radio(chemo)therapie postoperativ nach Piver II/III??

- postoperative Radio(chemo)therapie?
- adjuvante Chemo?
Methods and Materials: Eligible patients had Stage IB cervical cancer with negative lymph nodes but with 2 or more of the following features: more than one third (deep) stromal invasion, capillary lymphatic space involvement, and tumor diameter of 4 cm or more. The study group included 277 patients: 137 randomized to pelvic irradiation (RT) and 140 randomized to observation (OBS). The planned pelvic dose was from 46 Gy in 23 fractions to 50.4 Gy in 28 fractions.

**Fig. 1.** Cumulative risk of recurrences by treatment group: 24 RT patients and 43 OBS patients recurred, and 3 non–disease-related deaths in each group were treated as censored observations. RT significantly reduced recurrence risk ($p = 0.007$). OBS = observation; RT = irradiation.
Zervixkarzinom – adjuvante Radiootherapie

GOG 92, 277 pts.

**Progression-Free Survival**

![Graph showing progression-free survival by treatment group.](image)

- **RX Group**
  - Proportion Progression at 12 months: 0.1
  - Proportion Progression at 24 months: 0.05

- **PF Failed Total**
  - Proportion Progression at 12 months: 0.2
  - Proportion Progression at 24 months: 0.1

**Survival**

![Graph showing survival by treatment group.](image)

- **RT**
  - Proportion Surviving at 12 months: 0.9
  - Proportion Surviving at 24 months: 0.8

- **OBS**
  - Proportion Surviving at 12 months: 0.8
  - Proportion Surviving at 24 months: 0.7

**p=0.009, HR=0.6**

**p=0.07, HR=0.7**

**Beyond 6 years, only 4 disease-related deaths (2 RT, 2 OBS) occurred, and, hence, the convergence of the curves is the result of other causes!!**

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The disparity between recurrence results and survival results in this study is surprising, given that survival comparison usually parallels recurrence comparisons in locally advanced cervix cancer trials (1, 9). However, the sample size may have been too low. The study had 80% power to detect only risk reductions of 46% or greater in OS and did not find significant the 26% to 30% hazard reductions reported above.
Radiotherapy and chemoradiation after surgery for early cervical cancer (Review)

Roger J, Sia SXN, Lassley B, Byass A, D’Hulstien B.O.

*The Cochrane Collaboration*

### Analysis 1.4. Comparison 1 Radiotherapy versus no further treatment, Outcome 4 Disease recurrence within 5 years (unadjusted).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Radiotherapy</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>N(Rrandom/95% CI)</td>
<td>N(Rrandom/95% CI)</td>
</tr>
<tr>
<td></td>
<td>197/200</td>
<td>3/63</td>
<td>1.00 [0.42, 2.76]</td>
<td>0.58 [0.37, 0.91]</td>
</tr>
</tbody>
</table>

Total events: 24 (Radiotherapy), 42 (Control)

Heterogeneity: Tau² = 0.0, Chi² = 0.52, df = 1 (P = 0.47; 95% CI = 0.10%

Test for overall effect: Z = 2.36 (P = 0.018)

Test for subgroup differences: Not applicable
- 268 pts., Stage FIGO IA2, IB, IIA

- radical hysterectomy and pelvic lymphadenectomy, who had risk factors as:
  - positive pelvic lymph nodes and/or
  - positive margins (R1) and/or
  - microscopic involvement of the parametrium
**GOG 109/SWOG 8797/RTOG 91-12**

**268 pts.**

<table>
<thead>
<tr>
<th>RANDOMIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT (49.3 Gy)</td>
</tr>
<tr>
<td>vs.</td>
</tr>
<tr>
<td>RCT (49.3 Gy) + Cisplatin 70 mg/m² bolus 5-FU 1000 mg/m² x 4 d</td>
</tr>
</tbody>
</table>

every 3 weeks for **four cycles**, with the first and second cycles given concurrent to RT.

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**RAPID PUBLICATION**

Concurrent Chemotherapy and Pelvic Radiation Therapy Compared With Pelvic Radiation Therapy Alone as Adjuvant Therapy After Radical Surgery in High-Risk Early-Stage Cancer of the Cervix


*J Clin Oncol 18:1606-1613. © 2000*
Zervixkarzinom – adjuvante Radiochemotherapie

GOG 109

268 pts.

Overall survival: 81% vs. 71%
Progression-free survival: 80% vs. 63%
Serious GIT side effects: 8 - 26%

Fig 2. Overall survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

Adjuvant Therapy After Radical Surgery in High-Risk Early-Stage Cancer of the Cervix

Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical–pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial

BJ Monk, et al.,

Gynecologic Oncology 96, 2005, 721-728

Survival of women with tumors >2 cm by treatment arm.
Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical–pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial

BJ Monk, et al.,

Gynecologic Oncology 96, 2005, 721-728
A randomized controlled study of single-agent cisplatin and radiotherapy versus docetaxel/cisplatin and radiotherapy in high-risk early-stage cervical cancer after radical surgery.

In conclusion, for postoperative patients with high-risk early-stage cervical cancer, TP-R cannot increase OS and RFS compared with C-R, although TP-R has the trend of increasing PFS. This trend is worth further investigation.

Fig. 2 Overall survival (OS) curves of the C-R and TP-R groups. The 5-year OS rate was 74.3% in the C-R group and 82.8% in the TP-R group. Differences in OS were not significant (P = 0.098 by a two-sided log-rank test).

Fig. 3 Recurrence-free survival (RFS) curves of the C-R and TP-R groups. The 5-year RFS rate was 69.3% in the C-R group and 79.3% in the TP-R group. Differences in RFS were not significant (P = 0.061 by a two-sided log-rank test).
The most reliable and unconfounded estimate of the effect of chemoradiotherapy alone is obtained from the 13 trials whose design did not include the use of additional chemotherapy. The HR for this group of 0.81 (95% CI 0.71 to 0.91) represents a highly significant (P < 0.001), 19% relative reduction in the risk of death with chemoradiotherapy compared with radiotherapy and translates to an absolute survival benefit of 6% at five years (from 60% to 66%).

The HR for the two trials that gave chemoradiotherapy plus adjuvant chemotherapy of 0.46 (95% CI 0.32 to 0.66, P < 0.001), represents a 54% reduction in the risk of death with this treatment and translates into an absolute survival benefit of 19% at 5 years (from 60% to 79%) (Kantarzic 2004 [80 pts.]; Peters 2000 [268 pts.]).
Zervixkarzinom – adjuvante Radiochemotherapie

Indikation - Empfehlung der AGO (2008):

- Tonnenkarzinom (> 4 cm)
- Tiefe Stromainvasion
- R1-resektion
- L1 oder V1
- pN+
- inadequate Lymphadektomie

Anmerkung:
Bedeutung von Anzahl und Kombination von diesen Risikofaktoren ist unklar.
Zervixkarzinom – adjuvante Radiochemotherapie

WARUM – wichtigste Risikofaktoren

Prognostic factors in FIGO stage IB cervical cancer without lymph node metastasis and the role of adjuvant radiotherapy after radical hysterectomy.
Ayhan A, Al RA, Baykal C, Demirtas E, Ayhan A, Yüce K.

393 patients, FIGO Ib

Results:
Tumor size, L1 and vaginal involvement were independent prognostic factors

Pieterse QD, Trimbos JB, Dijkman A, Creutzberg CL, Gaarenstroom KN, Peters AA, Kenter GG.

402 patients, FIGO I-IIa

Results:
1. Pathologic tumor size (> or =40 mm),
2. Invasion (> or =15 mm), and
3. L1,
were identified as the so-called high-risk (HR)

Postop. RT bei Pat. mit Tumor>4 cm, Infiltrationstiefe >15 mm und L1 verbessert signifikant das 5-y. cancer-specific survival (86% vs. 57%) und auch DFS (85% vs. 43%)!!
Zervixkarzinom – adjuvante Radiotherapie

**WARUM – wichtigste Risikofaktoren**

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics (n = 225).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 (24–72)</td>
</tr>
<tr>
<td>Parity</td>
<td>2 (0–8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.9 (17.1–30.3)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>IB1</td>
<td>201 (89.3)</td>
</tr>
<tr>
<td>IB2</td>
<td>24 (10.7)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>167 (74.2)</td>
</tr>
<tr>
<td>Non-squamous cell carcinoma</td>
<td>58 (25.8)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>40</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>18</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>124 (55.1)</td>
</tr>
<tr>
<td>2–3</td>
<td>44 (19.6)</td>
</tr>
<tr>
<td>3–4</td>
<td>33 (14.7)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>24 (10.7)</td>
</tr>
<tr>
<td>Depth of stromal invasion (mm)</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td>135 (60.0)</td>
</tr>
<tr>
<td>11–15</td>
<td>59 (26.2)</td>
</tr>
<tr>
<td>16–20</td>
<td>20 (8.9)</td>
</tr>
<tr>
<td>21–</td>
<td>11 (4.9)</td>
</tr>
<tr>
<td>Lymph-vascular space invasion</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>124 (55.1)</td>
</tr>
<tr>
<td>Positive</td>
<td>101 (44.9)</td>
</tr>
<tr>
<td>Number of harvested lymph node</td>
<td></td>
</tr>
<tr>
<td>Pelvic</td>
<td>17 (2–60)</td>
</tr>
<tr>
<td>Para-aortic</td>
<td>6 (1–40)</td>
</tr>
</tbody>
</table>

**Table 2**

Univariate and multivariate analysis of various prognostic factors.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>168</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>57</td>
</tr>
<tr>
<td>Stromal invasion</td>
<td></td>
</tr>
<tr>
<td>≤10 mm</td>
<td>135</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>90</td>
</tr>
<tr>
<td>LVSI</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>124</td>
</tr>
<tr>
<td>Positive</td>
<td>101</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>168</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>57</td>
</tr>
<tr>
<td>Stromal invasion</td>
<td></td>
</tr>
<tr>
<td>≤10 mm</td>
<td>135</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>90</td>
</tr>
</tbody>
</table>

A validation study of new risk grouping criteria for postoperative treatment in stage IB cervical cancers without high-risk factors: Rethinking the Gynecologic Oncology Group criteria

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⁷Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, Republic of Korea
### Table 2. Results of the Univariate and Multivariate Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.0 0.96-1.02 .40</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>AC</td>
<td>2.7 1.5-4.9 .001</td>
<td>1.6 4.8 2.6-9.1 &lt;.001</td>
</tr>
<tr>
<td>ASC</td>
<td>2.8 1.0-8.2 .05</td>
<td>0.46 1.6 0.55-4.6 .40</td>
</tr>
<tr>
<td>Differentiation grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.6 0.39-7.1 .49</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>2.0 0.49-8.9 .33</td>
<td></td>
</tr>
<tr>
<td>Tumor diameter, mm</td>
<td>1.03 1.02-1.05 &lt;.001</td>
<td>0.02 1.02 1.0-1.04 .05</td>
</tr>
<tr>
<td>Depth of invasion, mm$^b$</td>
<td>1.6 1.3-2.0 &lt;.001</td>
<td>0.24 1.3 1.01-1.6 .04</td>
</tr>
<tr>
<td>Stromal invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;$1/3</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>1/3-2/3</td>
<td>3.4 0.89-13 .07</td>
<td></td>
</tr>
<tr>
<td>$&gt;$2/3</td>
<td>9.9 3.1-32 &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Vaginal wall extension macroscopic</td>
<td>1.5 0.69-3.1 .31</td>
<td></td>
</tr>
<tr>
<td>Parametrial extension present</td>
<td>5.6 3.2-9.6 &lt;.001</td>
<td>1.08 3.0 1.6-5.4 &lt;.001</td>
</tr>
<tr>
<td>LNM present</td>
<td>7.3 4.1-13 &lt;.001</td>
<td>1.2 3.3 1.8-6.1 &lt;.001</td>
</tr>
<tr>
<td>LVSI present</td>
<td>3.4 1.9-6.1 &lt;.001</td>
<td>0.85 2.3 1.2-4.5 .01</td>
</tr>
<tr>
<td>Surgical margins/spill positive</td>
<td>0.93 0.56-1.5 .77</td>
<td></td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; $\beta$, regression coefficient; SCC, squamous cell carcinoma; Ref, reference; AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; LNM, lymph node metastasis; LVSI, lymph vascular space invasion; DSS, disease-specific survival; TD, tumor diameter; DI, depth of invasion.

Prognostic Model for Survival in Patients With Early Stage Cervical Cancer

710 pts, FIGO IA2-IIA
Zervixkarzinom - Radiochemotherapie

SUMMARY

FACTS

FACTS

FACTS

FACTS
Simultane Radiochemotherapie

(*Cisplatin weekly oder Cisplatin/5-FU oder 5-FU/Mitomycin C*)

mit

Image-guided-Brachytherapie

gelten als

„Goldstandard-Therapie“ für FIGO II / III / IVa
Statement II.

Postoperative Strahlentherapie des Zervixkarzinoms

Bei Risikofaktoren:

- R1-Resektion,
- pN+,
- inadequate Lymphadektomie,
- Tonnenkarzinom (> 4 cm),
- tiefe Stromainvasion (>10-15 mm, >1/3),
- L1
- V1

ist eine postoperative **simultane Radiochemotherapie** *(Cisplatin weekly oder 5-FU/Cisplatin oder 5-FU/Mitomycin C)*

**Einer Standardtherapie.**
Strahlentherapie des Zervixkarzinoms

„...man muss es können...!“