Green Meta-analysis:
Role of Chemo RT in Cervical cancer

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• Update available. Cochrane database 2005
Methods

• RCT Ca Cx. FIGO Stage 1B-IV A
• All trials comparing Concurrent Chemotherapy +RT(±Surgery) vs RT (± Surgery) including those used adjuvant chemotherapy.
• Hydroxyurea considered inactive and acceptable in control group.

• Primary outcome. OS and PFS
• Secondary outcome. LR + DR and A/c + C/c toxicity
Results: Overall Survival

Figure 1: Results for overall survival
O–E = observed minus expected; HR = hazard ratio. *Number of events/number entered. †Unpublished data.
Results: Overall Survival

- 11 trials. 3656 randomized patients
- Overall survival. HR 0.71 (0.63-0.81) p = <.0001
- 29% reduction of risk of death
- 12% absolute improvement in survival (95%CI 8-16)
- Effect was more in trials with ≥70% stage 1 or 2 disease.
Results

• PFS. Absolute Improvement 13% (95% CI 13-19)

• LR. Reduced by Chemo RT. OR = 0.61 (95% CI 0.51-0.73)

• DR. Reduced by Chemo RT. OR = 0.57 (95% CI 0.46-0.77)
Toxicity

**Acute .**
- Haematological (WBC 16% Vs 8%, Platelet 1.5% Vs 0.2%, others 29% vs 1%)
- Gastrointestinal (9% Vs 4%)

**Late .**
- Good long term data lacking.
- 7 deaths. 1 control Vs. 4 related to chemo.
Discussion

• Different trials have different control arms
• Different inclusion criteria
Summary of individual trials

Keys et al, NEJM 1999

• 374 patients with 1B2 No.
  • Pelvic RT 45 Gy/25 # →30 Gy to Pint A Brachytherapy → Hysterectomy
  • Pelvic RT 45 Gy/25 # + concurrent cis-platin → 30 Gy to Point A Brachytherapy → Hysterectomy
• 3 year survival rates were 74 % RT alone and 83 % with CCRT (P=0.008 by the log-rank test)
Peters WA et al, JCO 2000

• 268 high risk post op patients
  • Pelvic RT .49.3Gy /29#
  • DDP+ FFU q 3w X 4 cycles + Pelvic RT
• Median FU 42 months
• 4 year survival 81% vs 71% favoring CCRT.
Morris M et al. NEJM .1999

- 403 patients 2B-4A, 1B/2A if >5cm or Pelvic LN+ve
  - Extended field RT 45Gy/25# →Brachytherapy
  - Pelvic RT 45 Gy/25# + DDP&FFU infusion Q3W →Brachytherapy
- 5 year survival 58% Vs 73% (for RT alone Vs CCRT)
Ross PG et al, NEJM 1999

526 patients 2B-4A PALN -Ve

- Weekly Cisplatin + Pelvic RT + Brachytherapy
- 2 cycles of Cisplatin + FFU + Hydroxyurea + Pelvic RT + Brachytherapy
- Hydroxyurea + Pelvic RT + Brachytherapy

- Median FU 35 months

- RR of death 0.61 (95% CI 0.44-0.85) in Group1 and 0.58 (95% CI 0.41-0.81) in group 2 compared to group 3.
Whitney CW et al, JCO 1999

- 388 patients with 2B-4A, PALN-ve
  - 2 cycles of DDP+ FFU infusion (4 W)+ Pelvic RT → Brachytherapy
  - Pelvic RT + HU → Brachytherapy
- Median FU 8.7 years
- RR of death for DDP+FFU was 0.75 (90% CI 0.58-0.95).
Pearcey R et al, JCO 2002

• 259 patients, 2B-4A, 1B-2B if > 5 cm or Pelvic LN+
  • Weekly DDP + Pelvic RT 45Gy/25# → Brachy 8GyX 3 or similar
  • Pelvic RT 45Gy/25# → Brachy 8GyX 3 or similar

• Median FU 82 months.
• 5 year Survival 62% Vs 58% . Not significant
• 62% v 58% (arm 1 v arm 2), respectively
Survival advantage

- 19% Relative risk reduction (of death)
- 6% absolute survival benefit at 5 years
- The benefit is more for earlier stages.
Benefit and disease stage.

Fig 2. (A) Survival and (B) disease-free survival by tumor stage (main group of 13 trials only). CTRT, chemoradiotherapy.
Survival advantage of 7.5% with CCRT in carcinoma cervix
10.4% excess acute toxicities - grade 3 or 4.
Indian Data. Nandakumar et al JGO 2015
Table 5 – Comparison of Survival Rates With Relevant Publications

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>FIGO Stage</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>5-Year OS (months)</th>
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<td>Randomized clinical trial</td>
<td>IB-IVA</td>
<td>RT</td>
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<td>Eifel et al²³</td>
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<td>RT</td>
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<td>RTCT</td>
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<td>Retrospective</td>
<td>IB2-IVA</td>
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</table>
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• For the 790 patients who had radical treatment, the five year survival probability is 70.3%. (2006-2008).

• The patients who had concurrent chemotherapy (two third of patients) did better (74.2% compared to 62.3%)
Summary

• There is sufficient evidence for benefit of concurrent chemotherapy with radiotherapy for carcinoma cervix
• The benefit is more for earlier stages than stage 3 or 4
• There is more acute toxicity.
• Data on long term toxicity inadequate.
• Value of adjuvant chemotherapy to be identified.
Thank you.