Landmark trials on advanced technology for cervical cancer

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Learning objectives ....

• To list the available trials on advanced technology

• To identify the limitations of conventional radiation

• To list the benefits of advanced technology

• To define the selected role of advanced technology for cervical cancer
Indian scenario...

- More than one lakh women are diagnosed with cervical cancer every year
- More than 90% of newly diagnosed patients require radiotherapy
- Huge burden of patients per machine and unequal distribution of facilities
- Only 25% of Indian population are medically insured
- Cost of the 3DCRT treatment is 40% more than that of 2DCRT but still 40% less than that of IMRT
- Brachytherapy contributes to the success of radiotherapy for cervical cancer
Standard treatment ...

- Concurrent chemoradiation with CDDP infusion... followed by ICBT/ISBT
- Mostly 3 DCRT and wherever not available conventional four field technique..
outcome with standard treatment ... 

- Control: 69-78 %
- Acute GI, gr III-IV: 7-16%, 49%, 81% for pelvic, extended pelvic and adding chemo... RTOG 0116
- Acute haemat... 76%
- Acute GU... 17%
- Chronic proctitis & cystitis... gr III & IV upto 40% with chemo
Landmark data...

  - comprehensive review
Where do we stand as far as IMRT for cervical cancer....

  - dosimetric evolution ....still in the nascent stage

- IntERECC over 20 institutes from all over the world, Survey of IMRT practice, Red Jou 81,2S 2011
  - Half of the participants saw only <50 cases a year
  - Majority used IMRT in the last 5 years.
Landmark trials mainly dosimetric....

  - Small bowel

  - Marrow

- Simpson DR et al. NTCP analysis of acute GI toxicity in cervical cancer undergoing IMRT and CDDP. REd Jou 2012;83(1):e81–6
  - GI toxicity

- Daniel et al, Red Jou,74,2,2009
  - SCR estimation
Simpson et al suggested that a decrease in V45 bowel by 100 CC reduces the gr 2 toxicity by 50 %
Mell suggested vol of marrow receiving 10-20 Gy predicts haematological toxicity

<table>
<thead>
<tr>
<th>Organ</th>
<th>V<strong>n</strong></th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel</td>
<td>V100</td>
<td>reduced by 50 %</td>
</tr>
<tr>
<td>Bladder</td>
<td>V100</td>
<td>reduced by 23 %</td>
</tr>
<tr>
<td>Rectum (as an IMRT Boost)</td>
<td>V66</td>
<td>reduced by 22%</td>
</tr>
<tr>
<td>Bladder (as an IMRT Boost)</td>
<td>V66</td>
<td>reduced by 19%</td>
</tr>
<tr>
<td>Bone marrow (BMS IMRT vs 3DCRT vs AP/PA)</td>
<td>V20</td>
<td>72 vs 97.8 vs 99 % (lesser gr 3 &amp; 4 toxicity)</td>
</tr>
</tbody>
</table>
Bowel sparing
Femora....spared
30 Gy sparing iliac crest and 45 Gy colour wash showing adequate coverage with sparing the marrow..
<table>
<thead>
<tr>
<th></th>
<th>2DCRT Median % (IQR)</th>
<th>3DCRT Median % (IQR)</th>
<th>IMRT Median % (IQR)</th>
<th>*p value</th>
<th>(A) - (B)</th>
<th>(A) - (C)</th>
<th>(B) - (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V40Gy (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bladder</td>
<td>98.7 (14.3)</td>
<td>91.2 (12.2)</td>
<td>69.9 (19.8)</td>
<td>&lt;0.001</td>
<td>0.078</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>V40Gy (%)</strong></td>
<td></td>
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<tr>
<td>Rectum</td>
<td>87.3 (11.7)</td>
<td>100 (0.8)</td>
<td>99.2 (15.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.477</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>V40Gy (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>Bowel Bag</td>
<td>20.05 (14.4)</td>
<td>28.9 (20.3)</td>
<td>22.6 (12.6)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.132</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>V20Gy (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bone marrow</td>
<td>84.6 (4.8)</td>
<td>93.0 (5.7)</td>
<td>72.04 (4.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>V40GY (%)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Left Femur</td>
<td>68.4 (13.7)</td>
<td>41.0 (19.0)</td>
<td>15.0 (12.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>V40GY (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Right Femur</td>
<td>63.7 (16.6)</td>
<td>35.9 (26.5)</td>
<td>13.5 (10.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2: Dose Volume Parameters of Bladder, Rectum, Bowel Bag, Femur and Bone Marrow in 2DCRT, 3DCRT and IMRT Treatment plans.

\*p value indicates the p value from Friedman test

#p value from post hoc Wilcoxon signed rank test after adjusting for multiple comparisons using Bonferroni adjustment
Landmark trials of dosimetric and clinical...

  - Bowel toxicity
  - Change in institutional policy
  - Dose escalation, bowel toxicity
- Klopp et al. Pt reported QOL Red Jou, 2016, 96, S3
- Loren et al. INTERTECC 2, Red Jou. 2017::97.3.
### Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Technique</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU gr II</td>
<td>IMRT vs 4 field</td>
<td>reduced from 91 to 60 %</td>
</tr>
<tr>
<td>Chronic GI</td>
<td>IMRT vs 4 field</td>
<td>reduced from 20 to 3 %</td>
</tr>
</tbody>
</table>
| Hematological (gr III)     | IMRT vs 3 DCRT | 24 % for pelvic  
28 % for para aortic (similar) |

Better sparing of bowel, bladder, rectum, bone marrow (especially as CDDP is also given) 
Probably translates to a better QOL
IMRT in terms of bone marrow sparing…

- InterTECC 2 ≥ gr III neutropenia 19.3% vs 40% (historical comparison), improved QOL at 4 mths

- Korean retrospective study..anaemia (21 vs 40% and gr I and II 56 vs 79% for IMRT and conventional respectively)

- Brixley..No significant sparing of iliac crest for doses > 30 Gy

Studied gr II-IV…however gr II is really not worrisome
Landmark trials for efficacy:

No randomised trials…Most are for adjuvant setting..

Results....

- No difference compared to 3DCRT as far as local failure, OS and DFS goes.
- Higher distant failure with IMRT...up to 27 %

Suggestion...
- With lesser toxicity, similar outcome, higher distant failure...is there a place for more chemo?
- Molecular biology?
Landmark trials for planning....

Better coverage...

- around 62% coverage superiorly and 49% posteriorly with conventional
- Mundt et al...>110% by 10% of PTV and >115% by 0.2% Vs 4 field

Better coverage of PTV /dose escalation
undercoverage.....of PTV
## Table 1: PTV (Planned Target Volume) Coverage in 2DCRT, 3DCRT, and IMRT.

*\( p \) value indicates the \( p \) value from Friedman test

\#\( p \) value from post hoc Wilcoxon signed rank test after adjusting for multiple comparisons using Bonferroni adjustment

<table>
<thead>
<tr>
<th>PTV Coverage (%)</th>
<th>2DCRT (A)</th>
<th>3DCRT (B)</th>
<th>IMRT (C)</th>
<th>*( p ) value</th>
<th>Statistical significance (( p ) value)#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min-Max (%)</td>
<td>73.10-90.10</td>
<td>98.60-100.00</td>
<td>96.60-100.00</td>
<td>&lt;0.001</td>
<td>(A)-(B)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>82.2% (9.6)</td>
<td>99.9% (0.7)</td>
<td>99.3% (1.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
• Agreement as far as cervix, uterus and nodes are considered.
• No agreement as far as margins, para, vaginal length, dose to OARs and acceptable homogeneity are considered.
• Taylor...uterus moves more than cervix (MRI based)

Suggestion...

- GTV to CTV 1.5-2 Cm, CTV to PTV 0.7 cm with soft tissue verification on all days.
- Best is to have empty rectum and full bladder on all days
Large tu shrinkage...

- Chen et al, Red Jou vol 87,2S 2013
  - repeat CT scan at mid treatment
  - Reduction in size by 42 %

Suggestion...
Needs to be replanned
Risk of second cancer...


Smaller area of high dose and larger area of smaller dose...
Secondary cancer risk estimation......
(common in large areas of smaller dose than small areas of larger dose)

• dosimetric, CT based estimation
• Effective dose X tissue weighting factor, models for risk calculation
• Compared 3DCRT (4 beams), IM 6 MV (9 beams) and IM 18 MV (9 beams) - kept upper and lower borders same
• 0%, 2% and 12% for 3DCRT, 6 MV and 18 MV respectively
• Large volume, higher MU, head leakage, collimator scatter, secondary neutrons (>10 MV)

Although theoretical, possibility is still there, everything needs to be looked into and weighed against the expected benefit.
Can IMRT Replace Brachy?

- Wahab et al et al, AGIMRT (Applicator guided IMRT), dosimetric, mean percent tumor volume getting the prescription dose was higher for the AGIMRT (90 vs 58, $p = 0.005$)
- conceptual advantages?

- Roeske, Mundt et al...
  - only up to 77-80 Gy can be delivered with IMRT, with increased rectal toxicity
IMRT vs Brachy....
DVH....
Other aspects of planning...

- Simulation related...not possible in prone and with immobilization, frog leg position..
- Longer time, higher MU
- Problems of inverse planning Vs human planner
- Stringent QA/expertise/cost
- Relatively lesser dose from EBRT (mostly from brachy)
When should IMRT be used...

- Postop
- gross nodes - pelvic & para aortic
- cases medically unfit for brachy
- Vault ca
- IBS
- residual and recurrent
Small Jr W et al. EF RT and ICBT with cisplatin and amifostine for cervical cancer with positive lymph nodes: results of arm II of (RTOG) 0116. Int J Gynecol Cancer 2011;21(7):1266–75.
Pelvic nodal boost
Previously treated

- University of Chicago...

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>Conventional</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr II enteritis</td>
<td>60%</td>
<td>91%</td>
<td>0.002</td>
</tr>
<tr>
<td>Gr I</td>
<td>34%</td>
<td>75%</td>
<td>0.001</td>
</tr>
<tr>
<td>Rarely needed medication</td>
<td>75%</td>
<td>35%</td>
<td>0.001</td>
</tr>
<tr>
<td>GU gr II</td>
<td>10%</td>
<td>20%</td>
<td>0.22</td>
</tr>
<tr>
<td>GI symp at 20 mths F/u</td>
<td>11.1%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>≥Gr II haematological</td>
<td>31%</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>
Dose escalation....MD Anderson...

- For gross nodes..
- Pelvic nodes upto 64 Gy, 2.2 Gy/Fr, 50 Gy to microscopic disease
- Para aortic upto 70 Gy
- 5 years NED
3DCRT vs IMRT....
Going forward...

- GCIG … Gynaec cancer Inter Group formation from all over the world
- Collaborate, identify the problems, fund, QA and do trials in next 2-3 years.
Ongoing...

- NCI 10-269, LN +ve cervical cancer,
- Protons/3 DCRT/IMRT
- Side effects, QOL, Survival
To Sum Up….

- Trials with longer follow up are slowly coming up
- Dosimetric studies have shown theoretical benefits
- Clinical benefits in terms of reduced enteritis are apparent
- NOT A SUBSTITUTE for brachytherapy
- Beneficial in selected cases.. Postop, gross nodes, para aortic, cases medically unfit for brachy, Vault ca, IBS, residual and recurrent lesions
whenever IMRT is done.

- Make sure your QA is precise
- Use adequate margins
- Respect the OARs, evaluate the plan systematically
- If margins are inadequate, do IGRT on all days
Learning objectives ....

• To list the available trials on advanced technology
• To identify the limitations of conventional radiation
• To list the benefits of advanced technology
• To define the selected role of advanced technology for cervical cancer
Any queries???