Dr. Wondemagegenhu Tigeneh
MD, M Med RT (WITS), FC Rad Onc (S.A)
ETHIOPIA
ADDISS ABABA
Prospective Randomized study comparing three fractionation regimens of HDR brachytherapy for treatment of uterine cervix stage IIB-IIIIB
Prospective Randomized study comparing three fractionation regimens of HDR...

Background

- Carcinoma of the uterine cervix is the second most common neoplasm in women worldwide and is the most frequent cancer among women in Africa, Asia and South America.

- It is the most common malignancy in South African black and coloured females with a lifetime (1 – 74 years) risk of 1 in 41 and the 2nd and 5th most common cancer in Asian and white females, respectively.
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- A number of studies have shown that HDR brachytherapy with concomitant chemoradiotherapy is safe and effective in the management of cervical cancer.

- Patel et al (1992), 412 patients diagnosed with stage III or large stage I and II, biopsy proven cancer of the cervix were treated with EBRT and then randomized to receive either HDR 18 Gy in 2 fractions of 9 Gy each or 35 Gy by continuous application of LDR brachytherapy.
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**OBJECTIVES**

- To compare the local control with the following 3 HDR brachytherapy fractionation regimens:
  - (a) 2 fractions of 9 Gy each;
  - (b) 3 fractions of 8 Gy each and
  - (c) 4 fractions of 6.5 Gy each, with concomitant chemo radiotherapy,
- To compare the normal tissue complication rate using these 3 regimes
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**Inclusion criteria**

- Biopsy proven carcinoma of the uterine cervix,
- Age above 20 and below 75,
- Performance status ECOG 0 up to 2
- HIV negative,
- Carcinoma of the cervix FIGO stage IIB (distal) and IIIB (early), and
- Reliability of the patient for follow up
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- All patients fulfilling the inclusion and exclusion criteria received 50 Gy in 25 fractions of EBRT, and were then, randomized to one of the following three Arms.
- Arm I.
  Patients received HDR brachytherapy of 4 fractions of 6.5 Gy each. The brachytherapy was given once weekly during the last 4 weeks of EBRT with concomitant chemotherapy.
- Arm II
  Patients received HDR brachytherapy of 3 fractions of 8 Gy per fraction to point A. The HDR brachytherapy was given during the last 3 weeks of external beam radiotherapy with concomitant chemotherapy.
- Arm III
  Patients received HDR brachytherapy of 2 fractions of 9 Gy per fraction. The brachytherapy was given weekly during the last 2 weeks of external beam radiotherapy with concomitant chemotherapy.
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- During treatment, the patients were assessed weekly for side effects.
  - Each HDR brachytherapy application was evaluated individually.
  - A rigid intrauterine tandem (nucleotron 6 cm, 4 cm, or 2 cm in length) and a ring applicator (nucleotron 3.4 cm, 3.0 cm, or 2.6 cm in diameter) with a rectal shield were used.
  - The length of the tandem and the diameter of the ring were individualized for each patient.
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- Transparencies of appropriate magnification indicating the isodose distributions were placed over the applicator image on the screen.
- This was used to check the isodose distributions. The rectum and the bladder points were calculated according to the ICRU 38 recommendations.
- From lateral radiograph, the anterior rectal wall was identified with the help of a radio-opaque balloon and the posterior wall of bladder was identified using an indwelling catheter with contrast material in its balloon.
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- The pelvic sidewall reference point was visualized on an anterior-posterior radiograph related to a fixed bony structure (acetabulum).

- The doses to critical organs (rectum and bladder)
  - calculated by measuring the distance from the applicator to ICRU reference points from the graph after correcting for the magnification factor.
  - The graph was plotted for each ring size and tandem length.
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<table>
<thead>
<tr>
<th>Arm</th>
<th>EBRT Dose Gy/fx</th>
<th>EBRT No. fx</th>
<th>HDR Dose Gy/fx</th>
<th>HDR No. fx</th>
<th>Gy_{10} Point A</th>
<th>LQED Gy_{10} to point A</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>25</td>
<td>6.5</td>
<td>4</td>
<td>103</td>
<td>86</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>25</td>
<td>8</td>
<td>3</td>
<td>103</td>
<td>86</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>25</td>
<td>9</td>
<td>2</td>
<td>94</td>
<td>78</td>
</tr>
</tbody>
</table>

F.x.-fraction, Gy.-Gray, No. number, LQED-Linear Quadratic Effective Dose
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Table 6: BED Gy₃ dose and to late responding tissue for three fractionation regimens

<table>
<thead>
<tr>
<th>Arm</th>
<th>Gy₃ dose to the Point A</th>
<th>70% of BED dose in Gy₃ to organ at risk</th>
<th>Late responding tissue LQED in Gy₃ at 2 Gy/fraction to organ at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>165</td>
<td>115</td>
<td>69</td>
</tr>
<tr>
<td>II</td>
<td>171</td>
<td>120</td>
<td>71</td>
</tr>
<tr>
<td>III</td>
<td>155</td>
<td>109</td>
<td>65</td>
</tr>
</tbody>
</table>

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- In this study, the treatment outcome and complication were assessed in each arm using the following criteria:
  - The local control of the disease by a Pap-smear at six months post treatment in each arm,
  - The effect of stage, age, ring application and duration of treatment on local control,
  - Toxicity in each arm,
  - The effect of age and number of fields treated on radiation induced toxicity,
  - The doses to the bladder and rectal reference points and their association with radiation induced toxicity.
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RESULTS

• Seventy-one patients were entered in the study
  • Three patients were excluded due to active non-malignant diseases.
  • One patient had active tuberculosis and 2 patients had severe skin reactions and herpes zoster. A repeated HIV test in the latter 2 patients confirmed that they were HIV positive.
  • Two patients withdrew following the first HDR application. And
  • Four patients didn’t come for subsequent check up
  • The remaining 59 patients were further analysed.
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Table 7. Distribution of patients by stage in each arm

<table>
<thead>
<tr>
<th>Arm</th>
<th>Stage IIIB (distal)</th>
<th>Stage IIIB (early)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>
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- **Treatment outcome**
- Fifty-nine patients completed the prescribed treatment and were evaluated.
  - Fifty-two had a good clinical response with negative Pap-smears at 6 months.
  - Seven patients had a positive Pap smear with clinical signs of persistence disease.
  - There was no statistically a significant difference in response for treatment in 3 arms with p value of 0.464.
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<table>
<thead>
<tr>
<th>Arms</th>
<th>Radiation induced grade 0-2 bladder toxicity</th>
<th>Radiation induced grade 3 &amp; 4 bladder toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>
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Table 12 Radiation induced rectal toxicity in each arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>Radiation induced grade 0-2 rectum toxicity</th>
<th>Radiation induced grade 3 &amp; 4 bladder toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>
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Number of Fields and Radiation Induced Grade 3 & 4 Bladder and Rectal Toxicity

No. of patients

<table>
<thead>
<tr>
<th>Number of Fields</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

(p = 0.001)
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The Relationship between BED Dose to the Rectum and Toxicity

- Degree of toxicity
- BED Gy3 dose to rectal reference point

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The relationship between BED dose to the bladder and degree of toxicity

Degree of toxicity

BED Gy₃ dose to the bladder
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<table>
<thead>
<tr>
<th>Arm</th>
<th>BED Gy\textsubscript{3} to bladder range</th>
<th>mean dose to bladder</th>
<th>Threshold Dose induced grade 3&amp;4 toxicity in Gy\textsubscript{3} to bladder</th>
<th>BED Gy\textsubscript{3} to rectum range</th>
<th>Mean dose to rectum</th>
<th>Threshold Dose induced grade 3&amp;4 toxicity in Gy\textsubscript{3} to rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>107-137</td>
<td>119</td>
<td>120</td>
<td>97-120</td>
<td>108</td>
<td>107</td>
</tr>
<tr>
<td>II</td>
<td>101-130</td>
<td>118</td>
<td>111</td>
<td>101-123</td>
<td>111</td>
<td>110</td>
</tr>
<tr>
<td>III</td>
<td>95-123</td>
<td>110</td>
<td>114</td>
<td>95-123</td>
<td>106</td>
<td>105</td>
</tr>
</tbody>
</table>
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Table 14. Incidence of grade 3 & 4 toxicity to the rectum and bladder depending on BED Gy3 dose in Arm during six months

<table>
<thead>
<tr>
<th>Site</th>
<th>Variable</th>
<th>Category Gy3</th>
<th>Incidence of grade 3&amp;4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>Total BED at rectal point</td>
<td>&lt; 105</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 105</td>
<td>10.2%</td>
</tr>
<tr>
<td>Bladder</td>
<td>Total BED at bladder point</td>
<td>&lt; 120</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 120</td>
<td>15%</td>
</tr>
</tbody>
</table>
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**CONCLUSION & RECOMMENDATION**

- Careful attention to normal tissue doses such as the rectum, bladder, and small bowel is important when brachytherapy is combined with concomitant chemo-radiotherapy regimen in the treatment of locally advanced cervical cancer.

- Two insertions of 9 Gy each HDR application was feasible with an acceptable complication rates and equivalent local control rates when compared with 6.5 Gy for 4 fractions and 8 Gy for 3 fractions.

- Careful attention to radiotherapy technique and planning, such as patient positioning and number of portals will minimize both acute and long term toxicity.

- **Recommendation:** need further follow up to see late effect of high dose per fraction with bigger number of patients