Conventional and conformal technique of external beam radiotherapy in locally advanced cervical cancer: Dose distribution, tumor response, and side effects

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Abstract. The objective of this study was to compare conventional and conformal techniques of external beam radiotherapy (EBRT) in terms of the dose distribution, tumor response, and side effects in the treatment of locally advanced cervical cancer patients. A retrospective cohort study was conducted on cervical cancer patients who underwent EBRT before brachytherapy in the Radiotherapy Department of Cipto Mangunkusumo Hospital. The prescribed dose distribution, tumor response, and acute side effects of EBRT using conventional and conformal techniques were investigated. In total, 51 patients who underwent EBRT using conventional techniques (25 cases using Cobalt-60 and 26 cases using a linear accelerator (LINAC)) and 29 patients who underwent EBRT using conformal techniques were included in the study. The distribution of the prescribed dose in the target had an impact on the patient's final response to EBRT. The complete response rate of patients to conformal techniques was significantly greater (58%) than that of patients to conventional techniques (42%). No severe acute local side effects were seen in any of the patients (Radiation Therapy Oncology Group (RTOG) grades 3–4). The distribution of the dose and volume to the gastrointestinal tract affected the proportion of mild acute side effects (RTOG grades 1–2). The urinary bladder was significantly greater using conventional techniques (Cobalt-60/LINAC) than using conformal techniques at 72% and 78% compared to 28% and 22%, respectively. The use of conformal techniques in pelvic radiation therapy is suggested in radiotherapy centers with CT simulators and 3D Radiotherapy Treatment Planning Systems (RTPSs) to decrease some uncertainties in radiotherapy planning. The use of AP/PA pelvic radiation techniques with Cobalt-60 should be limited in body thicknesses equal to or less than 18 cm. When using conformal techniques, delineation should be applied in the small bowel, as it is considered a critical organ according to RTOG consensus guidelines.

1. Introduction
Cervical cancer is the most common cancer in Indonesia. It has a high incidence in developing countries, with 75% of cases at a locally advanced stage [1-3]. Radiotherapy plays an important role in the management of locally advanced cervical cancer. It provides local control at a range from 58–87%, however, intrapelvic recurrences occur 23% of the time in stage II-B and 41% of the time in stage III-B. The highest recurrence distribution occurs in the lateral parametrium at 92% [4-7]. Complete response after external radiation is a predictor of treatment success. Pelvic radiation is generally used with plan-parallel antero-posterior/postero-anterior (AP/PA) or box systems. Tumor geometry can be determined using bone markers (a conventional technique) or three-dimensional (3D) anatomical
imaging (a 3D/conformal technique) [8]. Conformal techniques can decrease uncertainties in the planning and implementation of radiation. In addition, an inverse planning process may provide a higher dose volume to treat the tumor, according to the International Commission of Radiation Units and Measurements (ICRU) 50, 62, and 83, with minimal dosages and volumes to obtain high local control and low morbidity [9-16].

In terms of the survival rate, there is no significant difference between conventional and conformal techniques, although conventional techniques tend to show higher local failure due to inadequate margins [8,17,18]. In terms of acute side effects, the techniques show no significant differences [19]. In terms of cost, conformal techniques have a higher cost and require longer times than conventional techniques [12,18]. Currently, 23 radiotherapy centers exist in Indonesia, but most still use conventional techniques like external beam radiotherapy (EBRT). The Radiotherapy Department of Cipto Mangunkusumo Hospital has been equipped with a CT simulator and a 3D RTPS. From 2009–2011, of the 399 patients with stages II-B and III-B cervical cancer admitted since the end of 2009, 93% were treated using conventional techniques, and only 7% were treated using conformal techniques.

2. Materials and Methods
This study was a retrospective cohort study that assessed the dose distribution, tumor response, and side effects of conventional and conformal techniques used in EBRT to treat locally advanced cervical cancer. The subjects of this study were all cervical cancer patients who underwent EBRT before brachytherapy in the Radiotherapy Department of Cipto Mangunkusumo hospital. The inclusion criteria of this study were having Federation of Gynecology and Obstetrics (FIGO) stages IIB or IIBB cervical cancer, EBRT before brachytherapy, CT image data, a combination of concurrent chemotherapy and conventional chemotherapy or no concurrent chemotherapy, and a Karnofsky Performance Status score of 60–100. The exclusion criteria were having FIGO stage IIB after a hysterectomy or stage IIB with stage IIIA components, concurrent hypoxia modifier or target therapy, extended-field radiation therapy, brachytherapy between EBRT and the central block, no EBRT and/or chemotherapy less than 3 times, and recurrent cases. The data were analyzed using SPSS. The dose distribution (numerical data) in each technique was analyzed using an unpaired t-test. The tumor response and acute side effects were compared using a chi-square test or a Fisher’s test. The statistical significance was set to p < 0.05.

3. Results and Discussion
In total, 51 patients treated using conventional EBRT (25 cases with Cobalt-60 and 26 cases with a LINAC) and 29 patients treated using conformal techniques were recruited. Overall, 93% of the patients treated using conventional EBRT used an AP/PA portal, and 7% used a box system portal. Box system scan reduce radiation dosage and volume, especially in the rectum. However, not many advantages can be obtained in using box systems to treat locally advanced cervical cancer, especially using conventional techniques, as they cannot determine the extension limit of the tumor appropriately [9,20]. Thus, this technique is not used as the standard [10,11,21-23]. The distribution of clinical characteristics is shown in Table 1. An unequal distribution was observed in tumor size/diameter before radiation (p = 0.004), type of histopathology (p = 0.02), and management using either chemoradiation or radiation (p < 0.001). Chemoradiation treatment was used in 30% of the cases (24/80 cases).

Nearly half of the cases treated with conventional EBRT used Cobalt-60. However, the advantages of a LINAC have made the use of Cobalt-60 less attractive, especially in developed countries [24,25]. Some studies have shown that the use of Cobalt-60 is no longer precise according to the physical characteristics of their radiation beams, including their wide penumbra and penetration power, which have a maximum depth of 0.5 cm from the surface of the skin [4,24-26]. One researcher stated that, although the gamma beam characteristics of a Cobalt-60 plane are different from the X-ray beam characteristics of a LINAC plane, as long as radiation is carried out in patients with a body thickness
of at least 18 cm, the dose distribution obtained should be similar [4,27]. In this study, a mean separation of 17.7 cm was observed in 25 patients who received Cobalt-60 radiation. Patients with a separation greater than 18 cm showed a larger planning target volume (PTV) and D-max, resulting in more than 107% of the prescribed dose. The clinical studies in the literature do not consistently demonstrate that a LINAC is superior to Cobalt-60 in the terms of the radiation effectiveness in detecting cervical cancer [4]. A retrospective study in Brazil on the use of Cobalt-60 in detecting cervical cancer result obtained the survival rate, disease-free survival, local control rate, and advanced side effects in the use of Cobalt-60 in accordance with other literature. The study concluded that pelvic radiation using a box-system technique to a dose of 50 Gy using Cobalt-60 before brachytherapy was practical to apply in cervical cancer cases, especially in developing countries [4].

Distribution of Dose and Acute Tumor Response
Statistically, the dose distribution (D-mean CTV/PTV and V-95%) using Cobalt-60 in conventional techniques was significantly lower than that in using a LINAC in conventional and conformal techniques, but it still conformed with that specified by the ICRU 50 and 62, in that PTV was included in 95–107% of the prescribed dose (Table 2). These results are in accordance with that of a dose metric

### Table 1. Subject characteristics (n = 80)

| Characteristics       | Conventional Techniques (%) | Conformal Techniques (%) | Total |
|-----------------------|-----------------------------|--------------------------|-------|
|                       | Cobalt-60 n = 25            | LINAC n = 26             |       |
| Age (years)           | 50.32 ± 7.92               | 51.31 ± 8.66             | 50.52 ± 11.66 |
| Stage                 |                             |                          |       |
| II-B                  | 5 (20)                     | 7 (27)                   | 11 (38) |
| III-B                 | 20 (80)                    | 19 (73)                  | 18 (62) |
| Histopathology        |                             |                          |       |
| Non-SCC               | 1 (4)                      | 2 (8)                    | 8 (28) |
| SCC                   | 24 (96)                    | 24 (92)                  | 21 (72) |
| Histopathology        |                             |                          |       |
| differentiation       |                             |                          |       |
| Moderate              | 21 (84)                    | 20 (77)                  | 26 (90) |
| Poor                  | 4 (16)                     | 6 (23)                   | 3 (10) |
| Tumor size before EBRT|                             |                          |       |
| ≤4 cm                 | 7 (28)                     | 7 (27)                   | 19 (65) |
| >4 cm                 | 18 (72)                    | 19 (73)                  | 10 (35) |
| Hb levels before EBRT |                             |                          |       |
| ≤10                   | 2 (8)                      | 2 (8)                    | 2 (7) |
| >10                   | 23 (92)                    | 24 (92)                  | 27 (93) |
| Management            |                             |                          |       |
| Radiation only        | 23 (92)                    | 24 (92)                  | 9 (31) |
| Chemoradiation        | 2 (8)                      | 2 (8)                    | 20 (69) |
| Duration of EBRT (days)| 37 (33–66)                 | 37 (33–50)               | 37 (33–59) |
| KPS                   |                             |                          |       |
| 60–90*                | 2 (8)                      | 5 (19)                   | 9 (31) |
| Comorbidity           |                             |                          |       |
| None                  | 19 (76)                    | 15 (58)                  | 24 (83) |
| Available             | 6 (24)                     | 11 (42)                  | 5 (17) |

| Characteristics       | Total |
|-----------------------|-------|
| Management            |       |
| Radiation only        | 56    |
| Chemoradiation        | 24    |
| Duration of EBRT (days)| -     |
| 37 (33–66)            |       |
| 37 (33–50)            |       |
| 37 (33–59)            |       |
| KPS                   |       |
| 60–90*                | 16    |
| Comorbidity           |       |
| None                  | 58    |
| Available             | 22    |
study that demonstrated that conformal EBRT can cover the dose corresponding to the tumor adequately but might decrease the unused dose and critical organ volume [10-13,24,28,29].

Table 2. Distribution of target dosage/volume and conformity index

| EBRT Before Brachytherapy | D-mean CTV (%) | D-mean PTV (%) | V-95% (cc) | Conformity Index | p-value |
|---------------------------|----------------|----------------|------------|-----------------|--------|
| Cobalt-60 conventional techniques (n=25) | 97±1.7 | 96±1.2 | 941±223 | 2.03±0.5 | |
| LINAC conventional techniques (n=26) | 103±1.3 | 102±1.6 | 1301±222 | 2.44±0.8 | <0.001 |
| Conformal techniques (n=29) | 101±1.2 | 101±1.3 | 1506±446 | 1.02±0.02 | |

EBRT using a LINAC and conventional techniques provided a higher prescribed dose distribution compared to that using conformal techniques. However, conformal techniques provided isodose curves with a PTV coverage suitable to the tumor’s dimensions, as indicated by the conformity index of conformal techniques, which achieved a nearly ideal value of 1.02 compared to that of 2 of conventional techniques. From 80 cases, a complete response after EBRT was found in 47% (38/80) of the cases (38/80); an incomplete response was found in 53% (42/80) of the cases. An evaluation of complete responses after EBRT showed that conventional techniques (Cobalt-60/LINAC) resulted in a significantly lower amount of complete responses compared to conformal techniques at 21% (8/38) and 58% (22/29), respectively (Table 3). This is in accordance with dosimetric analysis that showed that conformal techniques provide a higher distribution of the prescribed dose and target volume (according to the ICRU 50, 62, and 83). These results were also in accordance with the basic hypothesis that conformal techniques improve local control through their ability to provide large doses for the right target volume with tolerated side effects [30]. The number of complete responses after EBRT using conformal techniques may also be influenced by the bias in chemo radiation distribution. A small tumor size before radiation (≤4 cm) was also found in higher numbers using conformal techniques.

Table 3. Distribution of tumor response after radiation compared to EBRT techniques before brachytherapy

| EBRT Technique                  | Complete Response n=38 | Incomplete Response n=42 | p-value |
|--------------------------------|------------------------|--------------------------|--------|
| Cobalt-60 conventional techniques | 8 (21)                | 17 (40)                  | <0.001 |
| LINAC conventional techniques      | 8 (21)                | 18 (43)                  |        |
| Conformal techniques             | 22 (58)               | 7 (17)                   |        |

In a statistical test of clinic pathological characteristics, several factors that influence tumor regression after EBRT were identified, including the stage and size of the tumor before EBRT. The clinical stage is an important prognostic factor in cervical cancer, as later disease stages result in lower therapy success rates [6,31]. In this study, tumors with a complete response in stages II-B and III-B were achieved in 74% and 37% of cases, respectively. The analysis showed that low clinical stages (II-B) can obtain a greater complete response (4.8 times) than higher stages. Tumor size is also an important prognostic [6]. It was proven tumor sizes ≤4 cm obtained a complete response in 64% (21/38) of the cases, which was 3 times higher than tumor sizes >4 cm. In other words, the distribution of tumor dose in any radiation technique is able to cover a small tumor volume (≤4 cm) adequately.
This study only assessed the complete response; thus, the local control, disease-free survival, and survival rate were not assessed. However, rapid regression in tumor volume until the tumor disappeared after EBRT was found to be an important predictor of successful therapy [7,22]. If a residual tumor still exists after EBRT, especially in the peripheral region, then brachytherapy is not able to provide an adequate dose, resulting in a high risk of local recurrence. Predictably, if the tumor size is \( \leq 4 \) cm before EBRT and obtains a complete response after EBRT, then brachytherapy is able to provide adequate dose coverage, thus providing a high local control and low metastatic risk. The results of a univariate analysis showed that tumor sizes <3 cm provided 92% local control, tumor sizes 3–5 cm provided 85% local control, and tumor sizes >5 cm provided 79% local control. The risk of metastatic changes in tumor sizes <3 cm was 10%, that in tumor sizes 3–5 cm was 15%, and that in tumor sizes >5 cm was 25% [6]. Meanwhile, a multivariate analysis showed that larger tumor size increased the risk of tumor recurrence 1.39 times [25].

Squamous cell carcinoma (SCC) provides a higher incomplete response rate compared to adenosquamous cell carcinoma, as it is influenced by bias related to the uneven distribution of histopathological variants. In this study, the dominant histopathological variant was CC followed by adenocarcinoma; only one case of adenosquamous cell carcinoma was seen. This is in agreement with other studies that were unable to identify the type of histopathology as a prognostic factor, as only a few cases of non-SCC were included.

### Distribution of Dose/Volume in Critical Organs and EBRT Side Effects

AP/PA techniques provide a similar dose distribution to the target and critical organs without the risk of side effects [17,23,32]. It was proven in a dosimetric study that AP/PA techniques provide a higher dose distribution and critical organ volumes compared to box-systems and conformal techniques [28,31,33]. This study showed that the dose distribution (D-mean, D-max) and volume in the urinary bladder (Table 4) and those in the rectosigmoid (Table 5) in conventional techniques (Cobalt-60/LINAC) were significantly higher than in conformal techniques.

#### Table 4. Dose distribution in the urinary Bladder

| EBRT Before Brachytherapy | D-mean in the Urinary Bladder (cGy) | D-max in the Urinary Bladder (cGy) | V-50 Gy in the Urinary Bladder (%) | p-value |
|---------------------------|-------------------------------------|------------------------------------|------------------------------------|---------|
| Cobalt-60 conventional techniques (n=25) | 4996±90 | 5197±122 | 75.9±2.95 | <0.001 |
| LINAC conventional techniques (n=26) | 5264±126 | 5303±594 | 96.4±10.6 | <0.001 |
| Conformal techniques (n=29) | 4677±350 | 5247±156 | 31.9±29.7 | <0.001 |

#### Table 5. Dose distribution in the rectosigmoid

| EBRT Before Brachytherapy | D-mean in the Rectosigmoid (cGy) | D-max in the Rectosigmoid (cGy) | V-50 Gy (%) | p-value |
|---------------------------|---------------------------------|---------------------------------|-------------|---------|
| Cobalt-60 conventional techniques (n=25) | 4902±132.9 | 5259±76.87 | 72.7±23.5 | <0.001 |
| LINAC conventional techniques (n=26) | 5058±196.3 | 5430±149.4 | 90.5±12 | <0.001 |
| Conformal techniques (n=29) | 4810±302.5 | 5235±120.3 | 47±29 | <0.001 |

The dose distribution and volume coverage of critical organs using conventional techniques with Cobalt-60 were low, probably because Cobalt-60 provides a lower dose on the edge of the radiation field, resulting in the volume of critical organs receiving less radiation. Meanwhile, the D-max of the urinary bladder and that of the rectosigmoid in conformal techniques were relatively large and not significantly different from those in conventional techniques using Cobalt-60. This is likely because some posterior parts of the urinary bladder and/or anterior parts of the rectum are covered as the target in CTV (especially in stage III-B cervical cancer with infiltration to the uterosacral and cardinal...
ligaments); thus, the urinary bladder and rectosigmoid receive a high dose. This is in accordance with an evaluation study of conformal technique radiation planning (using beam’s eye view) that demonstrated that a part of the rectum was included in the dose coverage and target volume in 19 of 20 patients, as well as parametrical involvement in more than half of the patients [26].

The D-max and V-50Gy in bowel loops treated using conformal techniques were lower compared to those treated using conventional techniques; however, the D-mean in bowel loops treated with conformal techniques was higher (Table 6). This is likely a result of the bowel loop not being delineated as a critical organ. Delineation and dose limits are expected to decrease the D-mean in conformal techniques, as found in some dosimetric studies that obtained a decreased D-mean in the bowel using Intensity-modulated radiation therapy (IMRT) techniques compared to that using conventional or box-system techniques [28,34].

Table 6. Dose distribution in bowel loops

| EBRT Before Brachytherapy | D-mean in Bowel Loops (cGy) | D-max in Bowel Loops (cGy) | V-50 Gy in Bowel Loops (%) | p-value |
|---------------------------|-----------------------------|-----------------------------|----------------------------|---------|
| Cobalt-60 conventional techniques (n=25) | 2156±697 | 5240±115 | 20±21.3 | 0.013 |
| LINAC conventional techniques (n=26) | 2028±1174 | 5441±108 | 27.7±20 | |
| Conformal techniques (n=29) | 2928±700 | 5306±121 | 12.2±15 | |

No severe acute local side effects (RTOG grades 3–4) were detected in the cases in this study. The proportion of mild side effects (RTOG grades 1–2) in the gastrointestinal tract, urinary bladder, and skin were significantly higher when using conventional techniques in EBRT than when using conformal techniques at 72%, 78%, and 78% compared to 28%, 22%, and 28%, respectively (Table 7). Conformal techniques were found to result in less side effects (RTOG grade 0) in the gastrointestinal tract (59%), urinary bladder (46%), and skin (54%). A dosimetric study showed that conformal techniques resulted in decreased radiation doses and volumes in critical organs [10,21,31,35]. Several studies have shown these advantages clinically [29,36]. This study also showed that less side effects were seen in patients treated using conformal techniques than those treated using conventional techniques (Cobalt-60/LINAC). Analysis showed that the distribution of dose/volume in the bowel and in the rectosigmoid using conformal techniques were significantly lower compared to those using conventional techniques. More side effects in the skin were found when using Cobalt-60 conventional techniques (40%) than when using conformal techniques (22%), likely due to the physical characteristics of Cobalt-60, which only allow it to achieve a 0.5 cm depth from the surface of the skin [24,25]. Low side effects in the skin were seen when using conformal techniques (54%); mild side effects were experienced in RTOG grade 1.

Table 7. Distribution of Side Effects in the Lower Gastrointestinal Tract, Urinary Bladder, and Skin Resulting from EBRT Techniques

| EBRT Technique | Lower Gastrointestinal Tract (%) | Urinary Bladder (%) | Skin (%) |
|----------------|---------------------------------|--------------------|---------|
|                | None | R | p-value | None | R | p-value | None | R | p-value |
| Cobalt-60 conventional techniques (n=25) | 3 (14) | 22 (38) | | 12 (25) | 13 (41) | | 7 (20) | 18 (40) | |
| LINAC conventional techniques (n=26) | 6 (27) | 20 (34) | 0.02 | 14 (29) | 12 (37) | 0.03 | 9 (26) | 17 (38) | 0.01 |
| Conformal techniques (n = 29) | 13 (59) | 16 (28) | | 22 (46) | 7 (22) | | 19 (54) | 10 (22) | |
In addition to the radiation technique used, several clinicopathological factors were shown to affect the amount of side effects experienced; in other words, radiation (48%) resulted in significant (p = 0.02) side effects on the urinary bladder compared to chemoradiation (21%). In addition, patients <50 years of age (71%) experienced significantly (p = 0.02) higher side effects than those ≥50 years of age (46%). Chemoradiation increased the occurrence of radiation side effects, especially on the gastrointestinal tract and the urinary bladder [31,37]. However, the results of this study did not show any increased side effects in the gastrointestinal tract or the urinary bladder in the management of chemoradiation. This is in accordance with the finding that the distribution of radiation dose and volume in the rectosigmoid, bowel loops, and urinary bladder was low in patients treated with conformal techniques, most of which were chemoradiated (69%).

4. Conclusion
From this study, it can be concluded that the application of conformal pelvic radiation is highly recommended in radiotherapy centers equipped with CT simulators and 3D RTPs to decrease uncertainties in the radiation planning process. AP/PA pelvic radiation techniques using Cobalt-60 should be limited for use in patients with a body thickness equal to or less than 18 cm. In conformal techniques, delineation should be performed on the distal small bowel, as it is a critical organ according to RTOG consensus guidelines. A prospective study should be conducted to assess the dosimetry study of EBRT, therapeutic response, and side effects in order to determine the radiation technique or clinical application that should be used as a standard in the field.

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