Radiation or chemoradiation: initial utility study of selected therapy for local advanced stadium cervical cancer

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Abstract. This study aimed to compare radiation only or chemoradiation treatment of local advanced cervical cancers by examining the initial response of tumors and acute side effects. An initial assessment employed value based medicine (VBM) by obtaining utility values for both types of therapy. The incidences of acute lower gastrointestinal, genitourinary, and hematology side effects in patients undergoing chemoradiation did not differ significantly from those undergoing radiation alone. Utility values for patients who underwent radiation alone were higher compared to those who underwent chemoradiation. It was concluded that the complete response of patients who underwent chemoradiation did not differ significantly from those who underwent radiation alone.

1. Introduction
Globocan 2008 stated that cervical cancer was ranked 3rd of all malignancies in women and 7th of all malignancies worldwide [1]. The National Hospital Centre Cipto Mangunkusumo, Indonesia, (RSCM) found that as many as 76.7% of patients with cervical cancer presented at an advanced stage (≥ stage IIB) [2,3]. In 1999, the National Cancer Institute, USA, (NCI) recommended a combination of radiation and concurrent chemotherapy for the treatment of local advanced cervical cancer.

This was based on five randomized clinical trials that showed that radiation with concurrent chemotherapy (chemoradiation) resulted in better survival rates of local advanced cervical cancer [4]. However, the success of this therapy is currently unsatisfactory and controversial especially in developing countries. Therefore, this study examined the results of radiation only or chemoradiation treatment for local advanced cervical cancers by analyzing the initial response of tumors and acute side effects, as well as conducting an initial assessment of value based medicine (VBM) by obtaining utility values for both types of therapy.

2. Materials and Methods
This was a retrospective cohort study designed to determine the clinical response of tumors and the acute toxicity of patients with advanced local cervical cancer undergoing radiation or chemoradiation, as well as comparing the two therapies and analyzing influential prognostic factors. A cross-sectional study was also undertaken to obtain utility values for both modalities using a utility questionnaire. Affordable populations were all patients with advanced local cervical cancer (IIB-IIIB) undergoing
treatment at the RSCM Radiotherapy Department. Compared to the total sampling size expected at the end of the study, the sample size obtained was sufficient to obtain above 80% strength.

Inclusion criteria comprised patients with advanced local cervical cancer (based on the International Federation of Gynecology and Obstetrics (FIGO) staging of anatomical pathologies IIB, IIIA, and IIIB) undergoing radiation therapy with a curative dose; chemoradiated patients who had undergone chemotherapy for at least three cycles who had not been participants in previous research; and patients who could be reached by telephone (for the utility study). Exclusion criteria comprised patients with comorbidities; patients whose medical records and data could not be traced or was incomplete; and patients who did not complete radiotherapy, complete follow-up, or were unable to communicate well.

3. Results and Discussion

3.1 Retrospective Cohort

In accordance with the inclusion criteria, the number of cases involved in the analysis was 210 consisting of 140 radiation only patients and 70 chemoradiation patients. The distribution of clinical characteristics is shown in Table 1. Response to therapy was differentiated into complete, partial, stable, and progressive based on the largest change in tumor dimension prior to treatment compared to three months after completion of therapy (Table 2).

Table 1. Distribution of clinical characteristics by type of therapy

| Clinical Characteristics | Radiation (n=140) | Chemo radiation (n=70) | Total | p-value |
|--------------------------|------------------|------------------------|-------|--------|
|                          | n %              | n %                    | n %   |        |
| Age                      | 51.6             | 50.7                   | 210   | 0.874  |
| SD                       | 9.3              | 8.7                    |       |        |
| Stadium                  |                  |                        |       |        |
| 2B                       | 59               | 42.1                   | 94    | 44.8   |
| 3                        | 81               | 57.9                   | 116   | 55.2   |
| Tumordimensions          |                  |                        |       |        |
| ≤4                       | 75               | 53.6                   | 110   | 52.4   |
| >4                       | 65               | 46.4                   | 100   | 47.6   |
| Histopathology types     |                  |                        |       |        |
| Squamous                 | 90               | 64.3                   | 142   | 67.6   |
| Adenocarcinoma           | 31               | 22.1                   | 41    | 19.5   |
| Adenosquamous            | 13               | 9.3                    | 19    | 9.0    |
| Small cell               | 2                | 1.4                    | 3     | 1.4    |
| Others                   | 4                | 2.9                    | 5     | 2.4    |
| Hb pre-radiation         |                  |                        |       |        |
| <10                      | 29               | 20.7                   | 45    | 21.4   |
| 10.0–11.9                | 61               | 43.6                   | 84    | 40.0   |
| ≥12                      | 50               | 35.7                   | 81    | 38.6   |
| KPS                      |                  |                        |       |        |
| 100–90                   | 114              | 81.4                   | 179   | 85.2   |
| 80–70                    | 26               | 18.6                   | 31    | 14.8   |
| OTT                      |                  |                        |       |        |
| ≤56 days                 | 48               | 34.3                   | 62    | 29.5   |
| 56 days                  | 92               | 65.7                   | 148   | 70.5   |

KPS: Karnofsky performance scale; OTT: outcome treatment time
Table 2. Response to therapy based on type of therapy

|                     | Complete | Partial |
|---------------------|----------|---------|
|                     | n        | %       | n       | %       |
| Radiation (n=140)   | 122      | 87.1    | 18      | 12.9    |
| Chemoradiation (n=70)| 64       | 91.4    | 6       | 8.6     |
| Total (n=210)       | 186      | 88.6    | 24      | 11.4    |

In the overall analysis, there was no significant difference in tumor response between radiation alone and chemoradiation. However, the percentage of patients undergoing more chemoradiation had a complete response. In India, Chufal et al. also performed an assessment of three months of post-intracavitary radio therapy response to locally advanced-stage cervical cancer for patients treated by radiation alone vs. radiation plus cisplatin (40 mg/m²/week) vs. radiation plus gemcitabine (300 mg/m²/week), and obtained complete response results for each type of therapy of 80%, 68.8%, and 93.2%, respectively. Based on their significance analysis, there was no difference in three-month post-treatment therapy responses between radiation alone and radiation plus cisplatin, with a p-value of 0.225 [5]. In a randomised phase III trial, the GOG compared radiotherapy with concurrent fluorouracil plus cisplatin versus hydroxyurea in stage IIB–IVA cervical cancer. This trial (GOG 851) showed an increased progression of free survival (P = 0.033), overall survival (67% versus 57%), and a better toxicity profile for the experimental arm compared to hydroxyurea [6,7]. However, the studies combined the results in general, and the final conclusion of all the studies found that concomitant chemoradiation therapy with cisplatin (cisplatin alone; cisplatin and 5-fluorouracil (5-FU); cisplatin, 5-FU and hydroxyurea (HU)) showed better results than just radiation therapy or with chemoradiation in a non-cisplatin-based combination [6–10]. However, a 6th major randomized study conducted by the NCI reported that chemoradiation did not significantly improve progression-free survival or overall survival [11].

From this result, we can see that chemoradiation with cisplatin when compared with radiation therapy alone did not show superiority in terms of 3-month post-treatment tumor response. This may have been caused by several factors such as the number of cycles of chemotherapy and long outcome treatment times (OTTs). In this study, the majority of the samples underwent chemotherapy for three cycles. This was related to the general state of the patient as governed by the side effects of previous chemotherapy that required longer recovery periods. Tharavichitkul et al. reported that there was poor local control in patients undergoing chemotherapy for less than six cycles, but there was no significant difference in disease-free survival and distant metastasis-free survival [12]. The chemoradiation (80%) in this study was prolonged by OTTs > 56 days. This may have been caused by acute side effects experienced by the patient that resulted in delayed radiation. Previous studies showed that a 1-day extension would result in a loss of local control of 1.2% that would further lead to lower survival [13,14].

The treatment side effects analyzed in this study were acute lower gastrointestinal, genitourinary, and hematology that were observed weekly up to three months after completion of treatment. These acute side effect categories are based on radiation therapy oncology group (RTOG) criteria. The data of side effects is shown in Tables 3, 4, and 5. In terms of the total number of patients, the percentage with grade 0 acute lower gastrointestinal, genitourinary, and hematology adverse effects was greater in those who underwent radiation alone (i.e., 15.0% vs. 17.1%, 64.3% vs. 62.9%, and 13.6% vs. 7.1%). There were no acute grade 4 side effects. Acute grade 3 hematologic side effects were found in a higher percentage of patients who underwent chemoradiation (60%) compared to radiation alone (40%). These results suggest that chemoradiation was tolerable. This concurs with Kirwan et al.’s systematic review of acute and advanced side effects of concurrent chemoradiation of cervical cancer. They concluded that the acute side effects of chemoradiation treatment are still acceptable given the survival advantage [15].
### Table 3. Lower gastrointestinal side effects by type of therapy

| Therapy               | Grade 0 | Grade 1 | Grade 2 | Grade 3 | p-value |
|-----------------------|---------|---------|---------|---------|---------|
|                       | n       | %       | n       | %       | N       | %       |
| Radiation (n=140)     | 21      | 15.0    | 28      | 20.0    | 89      | 63.6    | 2       | 1.4     | 0.459   |
| Chemo radiation (n=70)| 12      | 17.1    | 19      | 27.1    | 37      | 52.9    | 2       | 2.9     |         |
| Total (n=210)         | 33      | 15.7    | 47      | 22.4    | 126     | 60.0    | 4       | 1.9     |         |

### Table 4. Genitourinary side effects by type of therapy

| Therapy               | Grade 0 | Grade 1 | Grade 2 | p-value |
|-----------------------|---------|---------|---------|---------|
|                       | n       | %       | N       |         |
| Radiation (n=140)     | 90      | 64.3    | 16      | 11.4    | 0.954   |
| Chemo radiation (n=70)| 44      | 62.9    | 9       | 12.9    |         |
| Total (n=210)         | 134     | 63.8    | 25      | 11.9    |         |

### Table 5. Hematology side effects by type of therapy

| Therapy               | Grade 0 | Grade 1 | Grade 2 | Grade 3 | p-value |
|-----------------------|---------|---------|---------|---------|---------|
|                       | n       | %       | n       | %       | N       | %       |
| Radiation (n=140)     | 19      | 13.6    | 104     | 74.3    | 15      | 10.7    | 2       | 1.4     | 0.236   |
| Chemo radiation (n=70)| 5       | 7.1     | 51      | 72.9    | 11      | 15.7    | 3       | 4.3     |         |
| Total (n=210)         | 24      | 11.4    | 155     | 73.8    | 26      | 12.4    | 5       | 2.4     |         |

### 3.2. Utility Questionnaire

The questionnaire results identified 29 patients who could be included in this study. Fourteen patients had undergone radiation only and 15 had undergone chemoradiation (Table 6). After interviewing the research participants, an estimate of the utility values for both types of therapy was obtained. Utility value for radiation alone was 0.85 and 0.72 for chemoradiation. Utility values in this study describe a person's subjective functional situation (i.e., how the state of health or the current state of the disease affects daily activities). The reason for selecting the current state was to reduce recall bias. Jewell et al. analyzed utility values of early-stage cervical cancer and treatment options. From the results of their study, it appeared that patients who preferred less invasive therapy and chemoradiation scored lower, even when compared with surgery [16]. Based on the analysis of clinical characteristics between the two groups; there was no significant difference in clinical character. While, in the analysis of clinical characteristics, the relationship with utility value exhibited a significant difference in recurrence character. It appears that the presence or absence of recurrence can affect the difference in utility values obtained. In recurrent patients, it has a lower value. This was also shown by Shih et al. who analyzed utility values in breast cancer patients and concluded that patients with local and far-reaching recurrences have lower utility values [17]. Nafees et al. also found that patients with non-small cell lung cancer with progressive or moderate disease being treated with second-line chemotherapy also had low utility values [18].
Table 6. Distribution of clinical characteristics by type of therapy from utility questionnaire

| Variables       | Radiation (n=14) | Chemoradiation (n=15) | Total (n=29) | p-value |
|-----------------|------------------|------------------------|--------------|---------|
|                 | n                | %                      | n            | %       | n        | %       |
| Age             |                  |                        |              |         |
| <50 years       | 6                | 50.0                   | 6            | 50.0    | 12       | 41.4    | 0.876   |
| ≥50 years       | 8                | 47.1                   | 11           | 57.9    | 19       | 65.5    |         |
| Stadium         |                  |                        |              |         |
| 2B              | 8                | 42.1                   | 11           | 57.9    | 19       | 65.5    | 0.450   |
| 3               | 6                | 60.0                   | 4            | 40.0    | 10       | 34.5    |         |
| SD              | 7                | 53.8                   | 6            | 46.2    | 13       | 44.8    |         |
| Education       |                  |                        |              |         |
| SMP             | 3                | 75.0                   | 1            | 25.0    | 4        | 13.8    | 0.450   |
| SMA             | 3                | 30.0                   | 7            | 70.0    | 10       | 34.5    |         |
| S1              | 1                | 50.0                   | 1            | 50.0    | 2        | 6.9     |         |
| IRT             | 10               | 43.5                   | 13           | 56.5    | 23       | 79.3    |         |
| Work            |                  |                        |              |         |
| PNS*            | 2                | 66.7                   | 1            | 33.3    | 1        | 10.3    | 0.599   |
| Others*         | 2                | 66.7                   | 1            | 33.3    | 1        | 10.3    |         |
| Payment         |                  |                        |              |         |
| Jamkesmas/Gakin/JPS* | 2   | 33.3          | 4            | 66.7    | 6        | 20.7    |         |
| Jamkesda/SKTM*  | 5                | 55.6                   | 4            | 44.4    | 9        | 31.0    |         |
| Askes*          | 5                | 83.3                   | 1            | 16.7    | 6        | 20.7    | 0.144   |
| Cash            | 2                | 25.0                   | 6            | 75.0    | 8        | 27.6    |         |
| Post-therapy time |                |                        |              |         |
| <2 years        | 10               | 2.1                    | 3            | 23.1    | 13       | 44.8    |         |
| ≥2 years        | 4                | 1.3                    | 9            | 75.0    | 16       | 55.2    | 0.005   |
| Advanced effect |                  |                        |              |         |
| No              | 9                | 50.0                   | 9            | 50.0    | 18       | 62.1    | 1.000   |
| Yes             | 0                | 0.0                    | 3            | 100.0   | 3        | 10.3    |         |
| Recurrence      |                  |                        |              |         |
| No              | 14               | 53.8                   | 12           | 46.2    | 26       | 89.7    | 0.224   |

* merged in statistical analysis

The next stage of the VBM assessment determined quality adjusted life years (QALYs). QALYs were obtained by multiplying lifetime (in years) by utility value for certain states of health. From six randomized trials, a gynecologic oncology group (GOG) 12 trials with weekly cisplatin obtained a median survival of four years with chemoradiation when compared to standard therapy. Median survival for radiation alone (Morris et al.) was three years. From these results, it appears that chemoradiation provides an additional 0.33 QALYs. Cost calculations are required to establish if an intervention is cost effective. The result of the QALYs benefit does not make a significant difference. Where the cost of chemoradiation is more than radiation alone, chemoradiation appears to be meaningless in value (cost-effective) from the standpoint of economic health analysis. This preliminary review requires further study because the sample size was very small and may not represent the wider population.

4. Conclusion

It can be concluded from this study that the complete response in patients undergoing chemoradiation did not differ significantly to those undergoing radiation alone. The incidences of acute lower gastrointestinal, genitourinary, and hematology side effects in patients undergoing chemoradiation did not differ significantly from those undergoing radiation alone. Utility values for patients who had undergone radiation alone were higher compared to those who had undergone chemoradiation. The increase in QALYs was obtained for chemoradiation by taking into account the cost incurred.
Chemoradiation was not cost-effective when compared with radiation only. Further research is needed to compare overall survival, disease-free survival, and progression-free survival rates between radiation alone and chemoradiation. Further research is also required to perform adverse effect analysis comparing radiation alone to chemoradiation. In addition, further research that examines the value of utility, especially in local cervical cancer staging categories of certain health conditions, is also required.

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