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Radiotherapy response and related clinicopathological factors of patients with cervical cancer

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Abstract. The incidence of cervical cancer was still high in RSCM, and most patients exhibited advanced stage disease. For approximately 20–50% of these patients, radiotherapy did not achieve local tumor control. Achieving complete response and eradication of locoregional tumors in patients with cervical cancer should improve survival rates. Therefore, the purpose of this study was to determine the radiotherapy response, and related clinicopathologic characteristics of patients with cervical cancer at our hospital. We used secondary data from 123 patients with stage IIA-IIIB cervical cancer who underwent radiation therapy at our hospital from January, 2014 to December, 2015. We recorded age, body mass index, blood pressure, hemoglobin, blood leucocyte count, serum albumin, largest tumor diameter FIGO staging, and pathologic characteristics for each patient. During radiation until 3 months post radiation, we also noted any gastrointestinal, genitourinary, and hematologic side effects. Our results indicate that acute side effects were generally tolerable during and three months post radiation therapy. The clinicopathologic characteristic that significantly related to complete response was largest tumor diameter.

1. Introduction
According to WHO (2010), cervical cancer cases were the second most frequent cancer, and the seventh most frequent cancer, among all cancers worldwide [1]. In Indonesia, cervical cancer is the second most frequent cancer in females aged 15–44 years. At Cipto Mangunkusumo Hospital, there were 3112 cases of cervical cancer diagnosed in 2007, accounting for 75% of all gynecologic cancers [2]. In Indonesia, the high incidence of this disease poses health, economic, and social burdens, particularly for those who are directly affected.

Another problem is that most patients are admitted with advanced stage disease, associated with a relatively low survival rate. For advance stage-IIb disease and above, depending on the patient’s condition, radiation can be used interchangeably with chemoradiation. On their research, Iskandar et al. revealed that there was no difference in the response to radiotherapy among the patients with cervical cancer at Cipto Mangunkusumo Hospital who underwent radiation only, compared to chemoradiation [3]. On the other side, some previous studies in the same hospital showed that it was
more difficult for patients with cervical cancer to complete chemoradiation treatment, compared to radiotherapy alone [4]. Therefore, for most of these patients, radiation therapy could be a stand-alone treatment modality. However, local tumor control associated with radiotherapy remains low, ranging from 20% to 50%. Failure to achieve local tumor control increases morbidity and risk of distant metastases; however, if successful, survival rates may be increased by as much as 50% [5].

Prior studies examined factors influencing radiotherapy response. If these factors can be clearly identified and modified, it will improve our understanding of how to increase radiotherapy response, and subsequent survival. Acute side effects during radiotherapy may potentially make patients not want to continue treatment. Therefore, we sought to determine the response rate to radiotherapy, the incidence of acute side effects, and the relationship between routine and simple clinicopathologic characteristics [e.g., Body Mass Index (BMI), blood pressure, blood hemoglobin levels, blood leucocyte counts, serum albumin levels, tumor size, FIGO staging, and histopathology and grading of patients in our hospital with cervical cancer.

2. Methods
This historical cohort design used secondary data from patients seen at Cipto Mangunkusumo Hospital, Department of Radiotherapy, from January 2014 to December 2015. All the patients carried a diagnosis of cervical cancer. Subjects’ data were analyzed if the subject had been diagnosed with cervical cancer based on histopathology examination who planned to complete standard-protocol radiotherapy [external curative dose of 46–50 Gy (25 times) using gamma$^{60}$Co 1,2 megavolt and LINAC 4-10 Mega Volt, continued to brachytherapy using the after loading method HDR microselectron unit of $^{129}$I, dose 700cGy, three times on A-point]. Subjects were excluded if they had other primary tumors, or if their datasets were incomplete.

This study determined the number of subjects using rule of thumb procedures, with correction, and the result was 123 subjects needed for bivariate and multivariate analyses. The protocol of this study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital, No. 971/UN2.F1/ETIK/2015.

This study recorded patients’ pre-radiation clinical factors, such as age, BMI, blood pressure, hemoglobin level, blood leucocyte count, serum albumin, largest tumor diameter FIGO staging and pathologic characteristics (e.g., histopathology and grading). In addition, we noted any hematologic side effects, and side effects involving the gastrointestinal tract and genitourinary tract during the radiation protocol, up to three months post radiation. Evaluation of radiotherapy response was based on Response Evaluation Criteria in Solid Tumors. Stata 13 was used to analyze the collected data further.

3. Results
This study had 124 cases for further analysis. Tables 1 and 2 show the baseline characteristics. Of the 123 cases, 84 cases (68.29%) exhibited a complete response, 30 cases (24.39%) had a partial response, six cases (4.88%) had a stable response, and three cases (2.44%) were progressive (Figure 1). There were no gastrointestinal side effects (grade 0) for 99 cases (80.49%), 20 cases were grade 1 (16.26%), four cases were grade 2 (3.25%), and no cases were grade 3. For genitourinary side effects, 105 cases experienced no (grade 0) side effects (85.37%), 17 cases were grade 1 (13.82%), one case was grade 2 (0.81%), and no cases were grade 3. For hematologic side effects, 108 cases experienced no side effects (87.80%), 15 cases were grade 1 (12.20%), and no cases exhibited grade 2 or 3 side effects (Figure 2).
Table 1. Clinical characteristics of patients with cervical cancer who underwent radiation treatment from January 2014 to December 2015.

| Clinical Characteristics | n (%) | Mean ± SD | Median (min–max) |
|--------------------------|-------|-----------|------------------|
| Age (years):             |       |           |                  |
| 26–49                    | 51 (41.46) | 50 ± 9    | 51 (26–74)       |
| 50–74                    | 72 (58.54) |           |                  |
| Body mass index (BMI)    |       |           |                  |
| (kg/m²):                 |       |           |                  |
| <18.5                    | 10 (8.13) | 23.98 ± 4.77 | 23.7 (14.3–46.6) |
| 18.5–22.9                | 46 (37.40) |           |                  |
| ≥23                      | 67 (54.47) |           |                  |
| Blood pressure (mmHg):   |       |           |                  |
| Hypertension             | 43 (34.96) | 130.17 ± 19.50/79.68 ± 11.43 | 129 (90–189)/82(54–114) |
| No hypertension          | 80 (65.04) |           |                  |
| Blood hemoglobin level (g/dL): | |           |                  |
| <10                      | 12 (9.76) | 11.48 ± 1.45 | 11.3 (7.3–15.8) |
| ≥10                      | 111 (90.24) |           |                  |
| Blood leucocyte count (cell/mm³): | |           |                  |
| ≤10.000                  | 76 (61.79) | 9589 ± 4082 | 8480 (2960–19410) |
| >10.000                  | 47 (38.21) |           |                  |
| Serum albumin level (g/dL): | |           |                  |
| <3.5                     | 9 (19.15) | 3.99 ± 0.73 | 4.2 (1.27–4.89) |
| ≥3.5                     | 38 (80.85) |           |                  |
| Largest tumor diameter (mm): | |           |                  |
| <40                      | 45 (36.59) | 45.79 ± 40 (15–102) | 40 (15–102) |
| ≥40                      | 78 (63.41) | 18.78 |                  |
| FIGO Staging             |       |           |                  |
| Stage IIA                | 4 (3.25) | N/A | N/A |
| Stage IIB                | 42 (34.15%) | N/A | N/A |
| Stage IIIA               | 7 (5.69) | | |
| Stage IIIB               | 70 (56.91) | | |

Table 2. Pathology characteristics of patients with cervical cancer who underwent radiation treatment only during January 2014–December 2015.

| Pathology Characteristic | N (%) |
|--------------------------|-------|
| Histopathology type      |       |
| Squamous cell carcinoma  | 89 (72.36) |
| Adenosquamous carcinoma  | 9 (7.32) |
| Adenocarcinoma           | 24 (19.51) |
| Neuroendocrine           | 1 (0.81) |
| Differentiation (Grading)|       |
| Good                     | 44 (35.77) |
| Moderate                 | 58 (47.15) |
| Poor                     | 21 (17.07) |
Figure 1. Tumor response of patients with cervical cancer who underwent radiation treatment only from January 2014 to December 2015.

Figure 2. Incidence of acute side effects in patients with cervical cancer who underwent radiation treatment only from January 2014 to December 2015.

On bivariate analysis, factor p-values were count [p = 0.969; RR 1.00 (0.78–1.29)], FIGO staging (II vs III) [p = 0.526; RR 1.08 (0.85–1.38)], histopathology (squamous cell carcinoma vs non-squamous cell carcinoma) [p = 0.159; RR 1.18 (0.90–1.55)], and grading (p = 0.469) (Tables 3 and 4). On multivariate analysis, tumor diameter was statistically significant, with p = 0.036 [RR 2.64 (1.07–6.56)] (Table 5).

Table 3. Bivariate analysis for serum albumin levels.

| Serum Albumin (g/dL) | Complete Response (n = 34) | No Complete Response (n = 13) | p     | RR   | IK95% |
|----------------------|---------------------------|-------------------------------|-------|------|-------|
| <3.5                 | 5                         | 4                             | 0.198 | 0.73 | 0.44–1.20 |
| ≥3.5                 | 29                        | 9                             | Reff  |      |       |
**Table 4. Bivariate analysis.**

| Characteristics               | Complete Response (n = 84) | No Complete Response (n = 39) | P     | RR | CI 95% |
|-------------------------------|---------------------------|------------------------------|-------|----|--------|
| Age (years)                   |                           |                              |       |    |        |
| 26–49                         | 32                        | 19                           | 0.266 | 0.87 | 0.67–1.12 |
| 50–74                         | 52                        | 20                           | Reff  |    |        |
| Blood pressure                |                           |                              |       |    |        |
| Hypertension                  | 29                        | 14                           | 0.882 | 0.98 | 0.76–1.27 |
| Non-Hypertension              | 55                        | 25                           | Reff  |    |        |
| Blood hemoglobin level        |                           |                              |       |    |        |
| <10                           | 6                         | 6                            | 0.193 | 0.71 | 0.40–1.27 |
| ≥10                           | 78                        | 33                           | Reff  |    |        |
| Body mass index (BMI)         |                           |                              |       |    |        |
| Overweight                    | 48                        | 19                           | 0.397 | 1.06 | 0.83–1.34 |
| Non-overweight                | 38                        | 18                           | Reff  |    |        |
| Blood leucocyte count (cells/µL) |               |                              |       |    |        |
| ≤10.000                       | 52                        | 24                           | 0.969 | 1.00 | 0.78–1.29 |
| >10.000                       | 32                        | 15                           | Reff  |    |        |
| FIGO stage                    |                           |                              |       |    |        |
| Stage II                      | 33                        | 13                           | 0.526 | 1.08 | 0.85–1.38 |
| Stage III                     | 51                        | 26                           | Reff  |    |        |
| Largest tumor diameter (mm)   |                           |                              |       |    |        |
| <40                           | 36                        | 9                            | 0.034 | 1.30 | 1.03–1.63 |
| ≥40                           | 48                        | 30                           | Reff  |    |        |
| Histopathology type           |                           |                              |       |    |        |
| Carcinoma                     | 21                        | 13                           | 35.14 |    |        |
| Non-Squamous Cell Carcinoma   | 65                        | 24                           | 0.159 | 1.18 | 0.90–1.55 |
| Differentiation               |                           |                              |       |    |        |
| Good                          | 33                        | 11                           | 0.469 | N/A | N/A    |
| Moderate                      | 38                        | 20                           | 51.28 |    |        |
| Poor                          | 13                        | 8                            | 20.51 |    |        |

**Table 5. Multivariate analysis.**

| Variable                  | Koef. | OR  | SE  | p    | IK95% |
|---------------------------|-------|-----|-----|------|-------|
|                           |       | Min | Max |      |       |
| Hemoglobin                | −0.756| 0.47| 0.30| 0.230| 1.14  |
| Tumor diameter            | 0.973 | 2.64| 1.23| 0.036| 1.07  |
| Histopathology type       | −0.549| 1.73| 0.76| 0.213| 0.73  |
| Constant                  | −0.997|     |     |      |       |

4. Discussion

This study found that most patients (n = 84, 68.29%) experienced a complete response. Thus, the radiotherapy response appears relatively good, even though it is lower than that reported in a previous study (81.6% in 38 patients in 2009, reported by the Radiotherapy Division of Cipto Mangunkusumo Hospital) [6]. This difference could be linked to sample size and length of observation time. However, a study by Amin et al. at Dr Soetomo Hospital, Surabaya, found a similar result (70.4% with complete response, and no complete response in 29.6%) [7]. This success rate in Indonesian patients with cervical cancer should be further elaborated and analyzed, considering that the protocol and subject characteristics vary among centers.

In addition, this study also revealed that some subjects had low-grade acute side effects, and most experienced no side effects. In spite of the side effects, all the patients were able to complete the
treatment course. Compared to chemoradiation with the same effectivity, the radiation side effects were reportedly much more tolerable.

Age was as a clinical prognostic factor for local control and survival in some studies. Elantholi et al. revealed that age > 50 y was linked with higher rates of no residual tumor [8]. In our study, we found this result with younger patients; however, we still cannot prove a direct relationship with lower complete response. Clinically, 26–50-year-olds tended to exhibit decreased response, by 0.87 times, compared to those older than age 50. However, statistically, age is not a significant determinant of complete response.

Simple nutritional status, measured by BMI, indicated that most of our subjects were overweight to obese. This finding stands in contrast to the popular perception that advanced stage cancer patients are always malnourished. Furthermore, higher BMI in patients with advanced stage disease increases risk of mortality due to non-cancer related factors [9]. This study showed that there is no significant relationship between BMI and complete response. Albumin levels showed that most of our patients were not hypoalbuminemic. Clinically said, albumin levels < 3.5 g/dL tended to decrease response by 0.73 times, but remained statistically insignificant.

Previous studies showed that cancer lesion diameter > 4 cm were more difficult to treat, compared to smaller size tumors, due to the high association of these tumors with early onset distant metastasis [10]. Additionally, larger tumor size is often linked with radioresistant cells due to high rates of mutation [11]. Eiffel et al. studied 1526 patients who underwent radiation and found that the control rate was 97% for tumors < 5 cm and 84% for tumors 5–7 cm [12]. Our results indicated that tumor size < 40 mm was linked with better complete response (2.64 times) compared to tumors ≥ 40 mm, with statistically significant results on both bivariate and multivariate analyses.

More than half of the subjects in our study exhibited stage IIB disease. Many patients presented with late stage disease, potentially making treatment more difficult. This condition was different to India; Chufal et al.’s study showed that most patients were stage IIB [12]. In spite of fewer earlier stage patients in our study, we still had four patients with stage IIA disease who underwent radiation therapy, even though it was not our standard procedure to radiate these individuals. Three patients requested radiation treatment in lieu of surgery. One patient underwent laparotomy, but was found to have inoperable disease, and opted instead for continued radiotherapy. On bivariate analysis, we did not find a significant association between FIGO stage and radiotherapy response.

Squamous cell carcinoma was common within our study cohort, followed by adenocarcinoma. Garcia-Arias et al. had similar findings. Recently, there is an increasing incidence of adenocarcinoma but decreasing incidence of squamous cell carcinoma. This could be linked to better diagnostic classification, obesity, and younger age at diagnosis [13]. Reagen and Wentz stated that adenocarcinoma was less sensitive to radiation, leading to poor survival. Meanwhile Fletcher et al. also linked poor survival to myometrial invasion, sparing radiation in most treatments [14]. However, in our study, the squamous cell carcinoma group responded similarly to those with non-squamous cell carcinoma.

Cervical cancer prognosis is also linked to differentiation or grading. In our study, more subjects had good and moderate differentiation, similar to findings by Chufal et al. [12]. However, the difference in grading did not result in different radiotherapy responses.

5. Conclusion
Most of definitive-curative radiotherapy responses for patients with stage IIA-IIIB cervical cancer were complete (68.29%). Partial response was seen in 24.49%, stable response in 4.88%, and progressive response in 2.44%. The acute and common gastrointestinal, genitourinary, and hematologic side effects were tolerable during and three months post radiation therapy. The clinical characteristic that significantly related to complete response to radiotherapy was largest tumor diameter. Clinicopathological factors like age, BMI, blood hemoglobin level, blood leucocyte count, serum albumin level, FIGO stage, histopathology, and tissue differentiation were not significant.
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