

Research Article

Radiotherapy Response of Cervical Cancer Patients at a Tertiary Referral Hospital in Indonesia

Respon Terapi Radiasi Pasien Kanker Serviks pada suatu Rumah Sakit Rujukan Tersier

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Abstract

Objective: To investigate the response of radiotherapy and related clinicopathologic characteristics on cervical cancer patients.

Methods: This was a retrospective study. Subjects were patients diagnosed with cervical cancer stage IIA-IIIIB who had undergone radiation therapy based on standard protocol in our hospital, during the period of January 2014 to December 2015. The clinical factors of those patients, such as age, Body Mass Index, blood pressure, hemoglobin level, blood leucocyte count, serum albumin, largest tumor diameter, the International Federation of Gynecology and Obstetrics (FIGO) staging, as well as pathologic characteristic, i.e histopathology and grading were recorded. During radiation protocol until 3 months post radiation, we also noted any side effects of gastrointestinal tract, genitourinary tract, and hematologic. Evaluation of radiotherapy response was based on Response Evaluation Criteria in Solid Tumors (RECIST).

Results: A total of 123 subjects were enrolled in this study. 84 cases or 68.29% was complete response, 30 cases or 24.39% was partial response, 6 cases or 4.88% was stable response, and 3 cases or 2.44% was progressive. Based on gastrointestinal side effect, there was no side effect or grade 0 on 99 cases (80.49%), grade 1 on 20 cases (16.26%), grade 2 on 4 cases (3.25%), grade 3 on 0 case (0%). Based on side effect of genitourinary, there was no side effect or grade 0 on 105 cases (85.37%), grade 1 on 17 cases (13.82%), grade 2 on 1 case (0.81%), grade 3 on 0 case (0%). Based on hematologic side effects, there was no side effect on 108 cases (87.80%), grade 1 on 15 cases (12.20%), grade 2 on 0 case (0%), grade 3 on 0 case (0%). Largest tumor diameter was statistically significant, with $p=0.036$ (RR 2.64 (1.07-6.56))

Conclusion: The majority of definitive-curative radiotherapy response on cervical cancer stage IIA-IIIIB was complete (68.29%). Acute side effects involving the gastrointestinal, genitourinary, and hematologic system were commonly can be tolerable during and 3 months post radiation therapy. Clinicopathologic characteristics significantly associated with the complete response of radiotherapy was the largest tumor diameter.

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Keywords: largest tumor diameter, radiation response, radiation side effect

Abstrak

Tujuan: Respon terapi radiasi dan karakteristik klinis serta patologi yang berhubungan pada pasien kanker serviks di RSCM.

Metode: Penelitian kohort ini dilakukan dengan menggunakan data sekunder terhadap 123 pasien kanker serviks stadium IIA-IIIIB yang menjalani radiasi kuratif definitif sesuai protokol standar bulan Januari 2014-Desember 2015 di RSUPN Dr. Cipto Mangunkusumo. Dilakukan pencatatan karakteristik klinis dan patologis sebelum radiasi. Dicatat juga efek samping akut gastrointestinal, traktus genitourinaria, dan hematologis selama menjalani protokol radiasi sampai 3 bulan pascaradiasi. Data respon tiga bulan pascaradiasi lengkap berdasarkan klinis dan pemeriksaan ultrasonografi transrektal/transvaginal dicatat dan diklasifikasikan sesuai Response Evaluation Criteria in Solid Tumors (RECIST).

Hasil: Dari 123 kasus, 84 kasus (68,29%) diperoleh respon komplit, 30 kasus (24,39%) respon parsial, 6 kasus (4,88%) respon stabil, dan 3 kasus (2,44%) respon progresif. Berdasarkan efek samping akut gastrointestinal, tidak didapatkan efek samping (derajat 0) pada 99 kasus (80,49%), derajat 1 pada 20 kasus (16,26%), derajat 2 pada 4 kasus (3,25%), derajat 3 pada 0 kasus (0%). Berdasarkan efek samping akut genitourinaria, tidak didapatkan efek samping (derajat 0) pada 105 kasus (85,37%), derajat 1 pada 17 kasus (13,82%), derajat 2 pada 1 kasus (0,81%), dan derajat 3 pada 0 kasus (0%). Berdasarkan efek samping akut hematologis, tidak didapatkan efek samping (derajat 0) pada 108 kasus (87,80%), derajat 1 pada 15 kasus (12,20%), derajat 2 pada 0 kasus (0%), dan derajat 3 pada 0 kasus (0%). Didapatkan hubungan bermakna antara diameter tumor ($p=0,036$; RR 2,64; IK95 1,07-6,56) dengan respon radiasi komplit.

Kesimpulan: Gambaran respon radiasi kuratif definitif pada kanker serviks stadium IIA-IIIIB di RSCM adalah 68,29% respon komplit. Efek samping akut gastrointestinal, genitourinaria, dan hematologis pada umumnya tidak terjadi selama dan sampai 3 bulan pascaradiasi. Sebagian besar efek samping akut yang terjadi berderajat rendah. Terdapat hubungan bermakna antara diameter tumor terbesar dengan respon komplit radiasi. Tidak terdapat hubungan bermakna antara usia, Indeks Masa Tubuh, kadar hemoglobin, jumlah leukosit darah, kadar albumin serum, stadium FIGO, jenis histopatologis, dan derajat diferensiasi dengan respon terapi radiasi.

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Kata kunci: diameter tumor terbesar, efek samping radiasi, respon radiasi

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INTRODUCTION

According to the World Health Organization (WHO), cervical cancer cases was the second number of all women cancer and the seventh number of all cancer around the world in 2010.¹ In Indonesia, cervical cancer is the second number of woman of age 15-44 years old. At Dr. Cipto Mangunkusumo hospital, cervical cancer number was 3112 cases found in 2007, which account for 75% of gynecologic cancer.² These magnitude of the incidence in Indonesia will add more health, economic, and social burden in this country, particularly for those women.

Another problem is the majority of them admitted on advanced stage, with relatively low survival rate. On advanced stage-IIb and higher, radiation can be used interchangeably with chemoradiation depend on patient condition. On their research, Iskandar, et al revealed that there was no difference in radiotherapy response among cervical cancer patients at Dr. Cipto Mangunkusumo hospital who underwent radiation only compare to chemoradiation.³ On the other side, few studies done previously in same hospital showed that it was difficult to a cervical cancer patient complete her chemoradiation course of treatment compare to radiotherapy.⁴ Therefore, radiation therapy could be a main modality for most of these patients. However, local tumor control of radiotherapy is still not satisfied yet, ranging from 20 to 50%. Failure to achieve local tumor control would increase the morbidity and the risk of developing distant metastasis. However, if successful, the survival rate could be increased as many as 50%.⁵

Factors influencing the radiotherapy response had been questioned and studied previously in numerous centers. If such factors were clearly identified and modified, it will gain our understanding in increasing radiotherapy response and hence survival. An acute side effect during the course could potentially making the patient not to continue the treatment. Therefore, we conducted a research to find out response rate of radiotherapy, incidence of acute side effect, and relation of routine and simple clinicopathologic characteristic-i.e age, Body Mass Index (BMI), blood pressure, blood hemoglobine level, blood leucocyte count, serum albumin level, tumor size, International Federation of Gynecology and

Obstetrics (FIGO) staging, histopathology and grading-of patients in our hospital.

METHODS

This retrospective study used secondary data from cervical cancer patients, who came to Dr. Cipto Mangunkusumo hospital, department of radiotherapy, during January 2014 to December 2015. The data of the subject was included for further analysis if the subject had been already diagnosed with cervical cancer based on histopathology examination, planned to have radiotherapy only based on standard protocol, i.e external curative dose of 46-50 Gy (25 times) using gamma ⁶⁰Co 1,2 megavolt and LINAC 4-10 Mega Volt continued to brachytherapy using after loading method HDR microselectron unit of ¹²⁹I, dose 700cGy, three times on A-point. Subjects suffering other primary tumor as well as incomplete data were excluded.

The clinical factors of those patients prior to radiation, such as age, Body Mass Index, blood pressure, hemoglobin level, blood leucocyte count, serum albumin, largest tumor diameter FIGO staging and pathologic characteristic, i.e histopathology and grading were recorded. During radiation protocol until 3 months post radiation, we also noted any side effects of gastrointestinal tract, genitourinary tract, and hematologic. Evaluation of radiotherapy response was based on Response Evaluation Criteria in Solid Tumors (RECIST). The collected data was further analysed using Stata 13.

RESULTS

We had 123 cases for further analysis. The baseline characteristic is shown in table 1. Among 123 cases, 84 cases or 68.29% was complete response, 30 cases or 24.39% was partial response, 6 cases or 4.88% was stabile response, and 3 cases or 2.44% was progressive. Based on gastrointestinal side effect, there was no side effect or grade 0 on 99 cases (80.49%), grade 1 on 20 cases (16.26%), grade 2 on 4 cases (3.25%), grade 3 on 0 case (0%) Based on side effect of genitourinary, there was no side effect or grade 0 on 105 cases (85.37%), grade 1 on 17 cases (13.82%), grade 2 on 1 case (0.81%), grade 3 on 0 case (0%). Based on hematologic side effects, there was no side effect on 108 cases (87.80%), grade 1 on 15 cases (12.20%), grade 2 on 0 case (0%), grade 3 on 0 case (0%).

On bivariate analysis, p of each factors were age ($p=0.266$; RR 0.87 (0.67-1.12)), Body Mass Index ($p=0.397$), blood pressure classification ($p=0.658$; RR 0.98 (0.76-1.27)), largest tumor diameter ($p=0.034$; RR 1.30 (1.03-1.63)), hemoglobin level ($p=0.193$; RR 0.98 (0.76-1.27)), blood leucocyte 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 result (squamous cell carcinoma vs nonsquamous cell carcinoma) ($p=0.159$; RR 1.18 (0.90-1.55)), and grading ($p=0.469$) (Table 2). On multivariate analysis, tumor diameter was statistically significant, with $p=0.036$ (RR 2.64 (1.07-6.56)) (Table 3).

Table 1. Characteristics of Cervical Cancer Patients Underwent Radiation treatment only during January 2014 - December 2015

Characteristics	n (%)	Mean \pm SD	Median (min-max)
Clinical Characteristics Age (years):		50 \pm 9	51 (26-74)
26-49	51 (41.46)		
50-74	72 (58.54)		
Body Mass Index (BMI) (kg/m²):		23.98 \pm 4.77	23.7 (14.3-46.6)
< 18.5	10 (8.13)		
18.5 - 22.9	46 (37.40)		
\geq 23	67 (54.47)		
Blood pressure (mmHg):		130.17 \pm 19.50 / 79.68 \pm 11.43	129 (90-189) / 82 (54-114)
Hypertension	43 (34.96)		
No Hypertension	80 (65.04)		
Blood hemoglobin level (g/dl)		11.48 \pm 1.45	11.3 (7.3-15.8)
< 10	12 (9.76)		
\geq 10	111 (90.24)		
Blood leucocyte count (cell/mm³)		9589 \pm 4082	8480 (2960-19410)
\leq 10.000	76 (61.79)		
> 10.000	47 (38.21)		
Serum albumin level (g/dl) :		3.99 \pm 0.73	4.2 (1.27-4.89)
< 3.5	9 (19.15)		
\geq 3.5	38 (80.85)		
Largest tumor diameter (mm)		45.79 \pm 18.78	40 (15-102)
< 40	45 (36.59)		
\geq 40	78 (63.41)		
FIGO Staging		N/A	N/A
Stage IIA	4 (3.25)		
Stage IIB	42 (34.15%)		
Stage IIIA	7 (5.69)		
Stage IIIB	70 (56.91)		
PATHOLOGY CHARACTERISTICS			
Histopathology type		N/A	N/A
Squamous cell carcinoma	89 (72.36)		
Adenosquamous carcinoma	9 (7.32)		
Adenocarcinoma	24 (19.51)		
Neuroendocrine	1 (0.81)		
Differentiation (grading)		N/A	N/A
Good	44 (35.77)		
Moderate	58 (47.15)		
Poor	21 (17.07)		

Table 2. Bivariate Analysis

Characteristic		Complete Response		No Complete Response		p	RR	CI 95%
		n	%	n	%			
Age (years)	26-49	32	38.10	19	48.71	0.266	0.87	0.67-1.12
	50-7	52	61.90	20	51.29			
Blood pressure	Hypertension	29	34.52	14	35.90	0.882	0.98	0.76-1.27
	Non Hypertension	55	65.48	25	64.10			
Blood hemoglobin level	< 10	6	7.14	6	15.38	0.193*	0.71	0.40-1.27
	≥ 10	78	92.86	33	84.62			
Body Mass Index (BMI)	<i>Overweight</i>	48	55.81	19	51.35	0.397	1.06	0.83-1.34
	Non <i>overweight</i>	38	44.19	18	48.65			
Blood Leucocyte Count (cells/ μ l)	≤ 10.000	52	61.90	24	61.54	0.969	1.00	0.78-1.29
	> 10.000	32	38.10	15	38.46			
FIGO stage	Stage II	33	39.29	13	33.33	0.526	1.08	0.85-1.38
	Stage III	51	60.71	26	66.67			
Largest tumor diameter (mm)	< 40	36	42.86	9	23.08	0.034	1.30	1.03-1.63
	≥ 40	48	57.14	30	76.92			
Histopathology type	Squamous Cell Carcinoma	65	75.58	24	64.86	0.159	1.18	0.90-1.55
	Non Squamous Cell Carcinoma	21	24.42	13	35.14			
Differentiation	Good	33	39.29	11	28.21	0.469	N/A	N/A
	Moderate	38	45.24	20	51.28			
	Poor	13	15.48	8	20.51			
Serum Albumin Level	< 3.5	5	14.71	4	30.77	0.198*	0.73	0.44-1.20
	≥ 3.5	29	85.29	9	69.23			

*Fisher's exact test

Table 3. Multivariate Analysis

Variable	Coef.	OR	SE	p	IK95%	
					Min	Max
Hemoglobin	-0.756	0.47	0.30	0.230	0.14	1.61
Tumor diameter	0.973	2.64	1.23	0.036	1.07	6.56
Histopathology type	-0.549	1.73	0.76	0.213	0.73	4.11
Constant	-0.997					

DISCUSSION

The majority of the subjects had complete response, i.e 84 cases or 68.29%. This result showed that our radiotherapy response is relatively good, even though it is lower than previous study-i.e 81.6% - on 38 patients in 2009 reported by radiotherapy division of Dr. Cipto Mangunkusumo Hospital.⁶ The difference could be linked

to sample size and length of observation time. However, study by Amin, et al in Dr. Soetomo Hospital, Surabaya found similar result, i.e 70.4% and no complete response 29.6%.⁷ Whether this rate could be generalize as successful rate of radiotherapy response of cervical cancer patients in Indonesia should be further elaborated and analyzed, considering that the protocol and subject characteristics are still vary among centers.

This study also revealed that most of our subject had low grade acute side effect, most experience no side effect. All patient could complete the course of treatment regardless this side effect. It further stated that compare to chemoradiation with the same effectivity, the side effect of radiation is much tolerable.

Age has been shown as a clinical prognostic factor for local control and survival in some studies. Elantholi, et al revealed that age > 50 yo was linked with higher no residual tumor.⁸ In our study, more younger patient was found, but we still can not prove its direct relationship with lower complete response. Clinically, age group 26-50 yo tend to decrease response 0.87 times compare to age group > 50 yo. But statistically, age is not significant determinant for complete response.

Simple nutritional status measured by BMI showed that most of our subjects was overweight to obese. This finding against the perception that cancer patients on advanced stage was always malnourished. Furthermore, the higher BMI on advanced staged patients will add more risk of mortality due to non cancer related factors.⁹ This study showed that there is no significant relation between BMI and complete response. Albumin level as another way for measurement showed that most of our subjects was not in hypoalbuminemic state. Clinically said, albumin level < 3.5 g/dl tend to decrease response 0.73 times, but remain statistically insignificant.

Previous studies showed that cancer lesion diameter > 4 cm will be hard for being treated compare to smaller size due to high association with early onset distant metastasis.¹⁰ Additionally, larger tumor size often linked with radioresistant cells due to high rate of mutation.¹¹ Eiffel et al studied 1526 patients underwent radiation only found that control rate was 97% on tumor diameter < 5 cm and 84% on tumor diameter 5-7 cm.¹² Our finding showed that tumor size < 40 mm was linked with better complete response (2.64 times) compare to tumor size \geq 40 mm with statistically significant result on both bivariate and multivariate analysis.

More than half of subjects in our study was in the stage IIIB. It showed that there was still many patients came in late stage which was potentially making the treatment become difficult. This condition was different to India, as in Chufal et al's study showed that most of their patients was in

stage IIIB.¹² Regardless the fewer earlier stage in our subject, we still had 4 cases of stage IIA who underwent radiation therapy eventhough it was not our standard procedure to include them in radiation treatment. Due to patient preference to refuse surgery, 3 patients asked for radiation treatment. One patient had undergone laparotomy but found inoperable and further continued to radiotherapy. On bivariate analysis, we did not find significant association of FIGO stage with radiotherapy response.

Squamous cell carcinoma remains the most common type as in our study, followed by adenocarcinoma. Garcia-Arias, et all in their study also have similar finding. Recently there was increasing incidence of adenocarcinoma but decreasing incidence of squamous cell carcinoma. It could be linked to better diagnostic classification used, obesity, and more younger age at diagnosis.¹³ Reagen and Wentz stated that adenocarcinoma was less sensitive to radiation that lead to poor survival of such type. Meanwhile Fletcher, et al also believed that poor survival of such type was linked to miometrial invasion, thus it could spare the radiation in most of treatment.¹⁴ However, in our study, the response of radiotherapy of squamous cell carcinoma group was comparable to non squamous cell carcinoma.

Cervical cancer prognosis is also linked to differentiation or grading. In our study, more subjects was good and moderate differentiation, similar with findings by Chufal, et al.¹² On the other side, the difference in grading will not result in diferrence in radiotherapy response.

CONCLUSION

Most of definitive-curative radiotherapy responses on cervical cancer stage IIA-IIIB were complete (68.29%). Partial response was 24.49%, stable response was 4.88%, and progressive was 2.44%. The Acute side effects involving the gastrointestinal, genitourinary, and hematologic system could be tolerated during and 3 months post radiation therapy. The clinical characteristic that significantly related to complete response of radiotherapy was largest tumor diameter.

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