

Reirradiation on recurrent cervical cancer case: Treatment response and side effects

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Abstract. Management of recurrent cervical cancer by reirradiation after radiation treatment remains controversial. In Indonesia, there is currently no data about reirradiation tumor response and side effects. This study aims to assess the tumor response to and side effects of reirradiation, the effect of time interval between first radiation treatment and cancer recurrence on the tumor response and side effects, and the effect of tumor size on tumor response. A cohort retrospective study with no comparison was done with the Radiotherapy Department at Cipto Mangunkusumo General Hospital, Jakarta. Participants were recurrent cervical cancer patients undergoing reirradiation. Data was collected from patients' medical records and follow-up phone calls. Twenty-two patients participated in this study. Nine patients (40.9%) had complete responses, 10 patients (45.5%) had partial responses, 1 patient (4.5%) had a stable response, and 2 patients (9.1%) had tumor progressions. In general, 15 patients (68.2%) had no to light side effects (grade 0-2 RTOG) and 7 patients (31.8%) had severe side effects (grade 3-4 RTOG). Four patients (18.1%) had severe gastrointestinal acute side effects, 6 patients (27.3%) had severe gastrointestinal late side effects, 2 patients (9.1%) had severe urogenital side effects, and there were no patients had severe urogenital late side effects. There was no significant difference in tumor response between patients with time interval between first radiation treatment and recurrence of <12 months vs. ≥12 months. There was no significant difference in tumor response between patients with tumor size ≤4 cm vs. >4 cm. Reirradiation can be considered as a modality in recurrent cervical cancer management since good tumor response was achieved and the majority of patients had no to light side effects (grade 0-2 RTOG). This study found no correlation between tumor response, side effects, and time gap between first radiation treatment and recurrence of <12 months vs. ≥12 months. There was also no correlation between tumor response and tumor size of ≤4 cm vs. >4 cm.

1. Introduction

Cervical cancer is one of the most common malignancies in the world, especially in developing countries, ranking third of all malignancies present in women [1]. According to a study in 2008, cervical cancer is the second most common malignancy in Indonesian women [2]. Of cervical cancer patients who come to Cipto Mangunkusumo General Hospital (CMGH), 66.4% have advanced stage cancer, so treatment results are often disappointing [3]. The management of recurrent cases is based on



clinical decisions specific to each case. In general, the therapy chosen depends on the progression of the disease, the primary therapy given, the general condition of the patient, and their comorbidities, if applicable. Surgery, chemotherapy, and reirradiation on the pelvic area are alternative therapies. Reirradiation in Indonesia is still controversial as there is no data regarding the number of successes. In addition, side effects caused by reirradiation are considered in modalities. Therefore, this study aimed to obtain the number of successful treatments and side effects caused by reirradiation. Observations of the influence of time interval between initial treatment and recurrence on therapy response and side effects and the influence of tumor size on therapy response were also made.

2. Materials and Methods

This research used cohort retrospective studies without comparison to discover the therapy response and side effects of reirradiation on recurrent cervical cancer cases. The impact to results and side effects based on time intervals between first radiation therapy treatment and recurrence were assessed. The influence of the tumor size on reirradiation therapy response was also measured. The target population was recurrent cervical cancer patients undergoing reirradiation in Radiotherapy Department at CMGH. A total sample of 22 subjects fulfilled inclusion criteria. The inclusion criteria was recurrent cervical cancer patients, determined through clinical and/or pathological anatomy examination, undergoing reirradiation on the previous tumor area. The current tumor must have been found more than 6 months after first radiation and the patient must have a history of completed radiation therapy. The exclusion criteria was radiation in an area different from the previous radiation location. The obtained data was edited, coded, and entered using SPSS 13.0 for Windows. Descriptive analyses, in the form of frequency distribution, were performed on clinical characteristics. Bivariate analyses were used to examine the relationship between the time interval of the result with therapy response and side effects and the relationship between the tumor size with response therapy. The difference was determined via the logrank test. The significance limit was 0.05, so if $p < 0.05$, then there were statistically significant differences.

3. Results and Discussion

3.1 Results

There were 22 patients included in the study. Patient characteristics can be seen in Table 1. Reirradiation therapy response was differentiated into complete, partial, stable, and progressive based on the dimension changes of the largest tumor before and after therapy. Results are shown in Table 1. The relationship between the therapy responses with variables is shown in Table 2. The side effects of treatment analyzed were acute and advanced gastrointestinal and acute and advanced urogenital. The category of acute side effects was based on RTOG criteria, then grouped into no to mild acute side effects (RTOG grade 0-2) and severe side effects (RTOG grade 3-4). Advanced side effects were also grouped into no to mild advanced side effects (RTOG grade 0-2) and severe advanced side effects (grade 3-4). There were 15 patients (68.2%) who had no to mild side effects and 7 patients (31.8%) who had severe side effects. These results included both acute and advanced gastrointestinal or urogenital disturbances. The distribution of side effects are shown in Table 3.

The relationship between gastrointestinal acute side effects with reirradiation variables is shown in Table 4. The relationship between gastrointestinal advanced side effects with reirradiation variables is shown in Table 5. Relationship between urogenital acute side effects with reirradiation variables was shown in Table 6. There were no statistical significant relationship between vesical urinaria advanced side effect with reirradiation variables. There was a survival rate range between 2-52 months, with median patient survival of 7.5 months. Most found in 6-12 months groups.

Table 1. Patient characteristics

Characteristic	n	%
Age groups		
<50 years	8	36.4
≥50 years	14	63.6
Early tumor stage		
Stage I-b	1	4.5
Stage II-a	3	13.6
Stage II-b	11	50.0
Stage III-b	7	31.8
Tumor size before first radiation		
≤4 cm	8	36.4
>4cm	14	63.6
First histopathology		
SSC	14	63.6
Adenokarsinoma	5	22.7
Adenoskuamosa	2	9.1
Others	1	4.5
History of first radiation		
Radiation	8	36.4
Cheemoradiation	14	63.6
Type of first radiation		
Whole pelvis	4	18.2
Whole pelvis + brakhitherapi	18	81.8
Technique of first radiation		
2D AP PA	17	77.3
Box System	4	18.2
3D CRT	1	4.5
Diagnosis of reccurency		
Clinical	1	4.5
Imaging	4	18.2
Biopsy	2	9.1
Biopsy+imaging	15	68.2
Tumor size (when reccurent)		
<4 cm	19	86.4
>4 cm	3	13.6
Location of reccurency		
Cervix	15	68.2
Vagina	2	9.1
Other	5	22.7
Time interval of reccurency		
<12 months	3	13.6
≥12 months	19	86.4
Technique of reirradiation		
2D AP PA	6	27.3
Box	3	13.6
3D CRT	10	45.5
Brachytherapy	3	13.6
Dose of reirradiation		
≤40 Gy	8	36.4
50 Gy	8	36.4
>50 Gy	6	27.3
Reirradiation Therapy Response		
Complete	9	40.9
Partial	10	45.5
Stable	1	4.5
Progressive	2	9.1

Table 2. Relationship between the therapy responses with variables

Variable	Response n(%)		p-value
	Complete	Incomplete	
Recurrence interval			
<12 months	2 (66.7%)	1 (33.3%)	0.544
≥12 months	7 (36.8%)	12 (63.2%)	
Location of recurrence			
Cervix	6 (40%)	9 (60%)	1.000
Vagina/Others	3 (42.9%)	4 (57.1%)	
KPS Score			
90 – 100	9 (45%)	11 (55%)	0.494
70 – 80	0 (0%)	2 (100%)	
Histopathology of recurrence			
SSC	6 (42.9%)	8 (57.1%)	0.749
Adenokarsinoma	1 (16.7%)	3 (83.3%)	
Others	2 (50%)	2 (50%)	
Size of Recurrence			
≤4 cm	8 (42.1%)	11 (57.9%)	1.000
>4 cm	1 (33.3%)	2 (66.7%)	
Scope of radiation			
WP/WP + Brachytherapy	4 (57.1%)	3 (42.9%)	0.376
SmallPelvis/Brachytherapy	5 (33.3%)	10 (66.7%)	
Technique of radiation			
2D AP PA	1 (16.7%)	5 (53.3%)	0.333
3D CRT/Brachytherapy	8 (50%)	8 (50%)	
Dose of radiation			
≤ 40 Gy	4 (50%)	4 (50%)	0.662
≥50 Gy	5 (35.7%)	9 (64.3%)	

Table 3. Distribution of acute and advanced side effects of reirradiation

	n	%
Acute side effect of Gastrointestinal		
Grade 0	7	31.8
Grade 1	3	13.6
Grade 2	8	36.4
Grade 3	1	4.5
Grade 4	3	13.6
Advanced side effect of Gastrointestinal		
Grade 0	4	18.2
Grade 1	9	40.9
Grade 2	3	13.6
Grade 3	2	9.1
Grade 4	4	18.2
Acute side effect of Urogenital		
Grade 0	8	36.4
Grade 1	7	31.8
Grade 2	5	22.7
Grade 3	2	9.1
Advanced side effect of Vesica Urinaria		
Grade 0	11	50.0
Grade 1	10	45.5
Grade 2	1	4.5

Table 4. Relationship between gastrointestinal acute side effects with reirradiation variables

Variable	Side Effect		p-value
	No - Mild	Severe	
Recurrence interval			
<12 months	3 (100%)	0 (0%)	1.000
≥12 months	15 (78.9%)	4 (21.1%)	
Location of recurrence			
Cervix	12 (80%)	3 (20%)	1.000
Vagina/Others	6 (85.7%)	1 (14.3%)	
KPS Score			
90 – 100	18 (90%)	2 (10%)	0.026
70 – 80	0 (0%)	2 (100%)	
Size of recurrence			
≤4 cm	15 (78.9%)	4 (21.1%)	1.000
>4 cm	3 (100%)	0 (0%)	
Type of radiation			
WP / WP + Brachytherapy	5 (71.4%)	2 (28.6%)	0.565
Small Pelvis/Brachi	13 (86.7%)	2 (13.3%)	
Technique of radiation			
2D AP PA	3 (50%)	3 (50%)	0.046
Box System/3D CRT/BT	15 (93.8%)	1 (6.2 %)	
Dose of radiation			
≤40 Gy	6 (75%)	2 (25%)	0.602
≥50 Gy	12 (85.7%)	2 (14.3%)	

Table 5. Relationship between Gastrointestinal Advanced Side Effects with Reirradiation Variables

Variable	Side Effect		p-value
	Mild	Severe	
Recurrence interval			
<12 months	2 (66.7%)	1 (33.3%)	1.000
≥12 months	14 (73.7%)	5 (26.3%)	
Location of recurrence			
Cervix	12 (80%)	3 (20%)	0.334
Vagina/Others	4 (57.1%)	3 (42.9%)	
KPS score			
90 – 100	15 (75%)	5 (25%)	0.481
70 – 80	1 (50%)	1 (50%)	
Size of recurrence			
≤4 cm	13 (68.4%)	6 (31.6%)	0.532
>4 cm	3 (100%)	0 (0%)	
Scope of radiation			
WP/WP + Brachytherapy	4 (57.1%)	3 (42.9%)	0.334
Small Pelvis/Brachytherapy	12 (80%)	3 (20%)	
Technique of radiation			
2D AP PA	2 (33.3%)	4 (66.7%)	0.025
Box System/3D CRT/BT	14 (87.5%)	2 (12.5%)	
Dose of radiation			
≤40 Gy	6 (75%)	2 (25%)	1.000
≥50 Gy	10 (71.4%)	4 (28.6%)	

Table 6. Relationship between Urogenital Acute Side Effects with Reirradiation Variables

Variable	Side effects		<i>p</i> -value
	Mild	Severe	
Recurrence interval			
<12 months	3 (100%)	0 (0%)	1.000
≥12 months	17 (89.5%)	2 (10.5%)	
Location of recurrence			
Cervix	14 (93.3%)	1 (6.7%)	1.000
Vagina/Others	6 (85.7%)	1 (14.3%)	
KPS Score			
90–100	20 (100%)	0 (0%)	0.004
70–80	0 (0%)	2 (100%)	
Size of recurrence			
≤4 cm	17 (89.5%)	2 (10.5%)	1.000
>4 cm	3 (100%)	0 (0%)	
Scope of radiation			
WP/WP + Brachytherapy	6 (85.7%)	1 (14.3%)	1.000
Small Pelvis/Brachytherapy	14 (93.3%)	1 (6.7%)	
Technique of radiation			
2D AP PA	5 (83.3%)	1 (16.7%)	0.481
Box System/3D CRT/BT	15 (93.8%)	1 (6.3%)	
Dose of radiation			
≤40 Gy	7 (87.5%)	1 (12.5%)	1.000
≥50 Gy	13 (92.9%)	1 (7.1%)	

3.2 Discussion

For this study, 9 patients (40.9%) showed complete response, 10 patients (45.5%) showed partial response, 1 patient (4.5%) showed stable response, and 2 patients (9.1%) had a progressive tumor. Given that these cases were recurrent, the number of patients showing complete and partial responses is considered good. Research conducted in Korea by Kim *et al.* also obtained local control was high enough when finished the radiation, as much as 14 from 18 patients (78%) [4]. The Kim *et al.* research indicated that reirradiation therapy could be considered for patients with recurrent cervical cancer who had previous radiation, because it could give the sufficient positive response or local control. The majority of patients showed no to mild acute or advanced side effects, and there was no severe vesica urinaria side effects. Kim *et al.* found severe gastrointestinal and urogenital side effects such as bleeding from the rectum in 2 patients, bowel obstruction in 2 patients, and cystitis radiation in 2 patients [4]. Kim *et al.*'s data showed that although severe side effects could occur in some patients, there was higher in percentages of mild side effects, as seen in this study. Though several variable reirradiation conditions were observed (recurrence time intervals, location of recurrence, KPS score, histopathology, size of recurrence, type, and radiation dose), only KPS score at reirradiation related significantly with gastrointestinal acute side effects ($p = 0.026$). 100% (2/2) of patients with KPS scores of 70-80 had severe gastrointestinal acute side effects and 9.1% (2/22) of patients with KPS scores of 90-100 had severe acute gastrointestinal side effects. KPS score was also related significantly with acute urogenital side effects ($p = 0.004$), where in 100% (2/2) of patients with KPS scores of 70-80 had side effects of severe urogenital, while there were no patients with KPS scores of 90-100 suffered severe urogenital side effects [5]. By the status of performance, patients may be better at tolerating side effects.

There was a relationship between the radiation techniques and gastrointestinal acute side effects ($p = 0.046$). On the Box System/3D CRT/Brachytherapy technique of radiation found only one from

16 patients (6.2%) who had severe gastrointestinal acute side effects. While on 2D AP-PA technique, severe gastrointestinal acute side effects found in 3 of 6 patients (50%). Also found relationship between radiation technique with gastrointestinal advanced side effects ($p = 0.025$). On the Box System/3D CRT/Brachytherapy technique of radiation, found only two from 16 patients (12.5%) who had severe gastrointestinal advanced side effects, while on 2D AP-PA technique, found 4 out of 6 patients (Scored 66.7%) who had severe gastrointestinal advanced side effects. This showed that radiation technique that is more conformal (Box System/3D CRT/Brachytherapy) could minimise the acute and advanced side effects, especially on the gastrointestinal if compared with 2D AP-PA technique. Dearnaley *et al.* in randomised control trial research had been comparing the use of 3DCRT with 2D radiotherapy on the primary radiation prostate cancer [6]. The research showed the advantages of 3DCRT, conformal radiotherapy decreasing incidences of proctitis and rectal bleeding significantly compared with conventional radiotherapy.

There were only 3 patients that had <12 months interval of recurrence (8, 9 and 11 months) and there was no demonstrated relationship between the interval of recurrence with therapy response and side effects. Research by Kim *et al.* also did not find a significant relationship between intervals of recurrence with side effects [4]. Despite the small sample in our study, shorter intervals of recurrence may show differences in response to therapy and side effects. Further research is needed with a larger sample to see the relationship between intervals of recurrence and therapy response and side effects. Therapy response showed no significant relationships with any variables of reirradiation conditions (interval recurrence, location of recurrence, KPS score, histopathology, type, tumor size when recurrent, type and technique of reirradiation, and radiation dose). Xiang *et al.* found a significant difference in local control and survival between tumors <4 cm in diameter (32/37, 86.5%) and >4 cm (4/15, 26.6%) [7]. But in our research, there was not a statistically significant relationship between tumor size (≤ 4 cm and > 4 cm) with reirradiation therapy response. This might be due to small sample sizes (19 patients with tumor size ≤ 4 cm and 3 patients with tumor size > 4 cm). In our research, complete response was found in 8 out of 19 patients (42.1%) with ≤ 4 cm tumor size, and only 1 out of 3 patients (33.3%) with > 4 cm tumor size. Although there was no statistically significant relationship between tumor size and reirradiation therapy response, but there was a tendency toward better clinical response to therapy with the size of ≤ 4 cm.

4. Conclusion

This study showed no relationship between time intervals from initial radiation to recurrence of <12 months and ≥ 12 months and therapy response and side effects. There was no relationship between tumor size of ≤ 4 cm and > 4 cm and therapy response. However, there was a tendency for ≤ 4 cm tumors to better respond to therapy (8 out of 19 patients had better response). KPS score at reirradiation had a significant relationship with gastrointestinal and urogenital acute side effects. Patients with KPS scores of 70-80 had gastrointestinal acute side effects and more severe urogenital side effects compared to the patients with KPS scores of 90-100. The use of the 2D AP PA technique caused gastrointestinal acute and advanced side effects to be more severe compared with the use of more conformal techniques (Box System/3D CRT/Brachytherapy).

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