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Outcome and Radiotherapy Side Effects of High-Risk Endometrial Cancer

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ABSTRACT

The endometrial cancer is radiosensitive. Adjuvant radiotherapy is previously said that it may improve survival rate of high-risk endometrial cancer and decrease recurrences rate. This study evaluated overall survival, disease-free survival (DFS) in high risk endometrial cancer, and postradiotherapy side effects. Analytic retrospective research using medical record was conducted. During the 2013-2018 period there were 185 patients with endometrial cancer undergoing radiotherapy. Prognostic factors for OS which are statistically significant were age, BMI, LVSI, stage, waiting time interval, and recurrence. The prognostic factor group of age >60 years significantly had OS ($p = 0.04$) and DFS-3 years ($p = 0.03$) which was better than that of the age group <60 years. Obese patients had OS 77% better than the non-obese group ($p = 0.02$). The LVSI positive group significantly had OS 0% with OR of 0.3 (95% CI 0.1-0.8) ($p = 0.02$) and DFS-3 years 50% ($p = 0.004$). Patients with waiting time

intervals (queue) >9 weeks had OS 35% ($p = 0.03$) with OR of 3.2 (95% CI 1.1-8.8), and lower DFS-3 years (76% vs 91%; $p = 0.03$). Combination of radiotherapy modalities caused 61% of side effects, but statistically not significant. OS and DFS-3 years in patients >60 years old and obese were better than <60 years of age and non-obese. Positive LVSI group had poorer OS and DFS-3 years. The more side effects were due to the combination of modality.

Keywords: endometrium, high risk, radiotherapy

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INTRODUCTION

Endometrial cancer is one of the mortality causes of women worldwide with 200,000 new cases a year (1). The endometrial carcinomas are classified as Type I endometrioid endometrial carcinomas (EECs) and Type II non-endometrioid endometrial carcinomas (NEECs) (2,3). In 2016, there were 120 patients of endometrial cancer treated in dr. Soetomo Hospital, Surabaya (4). High-risk endometrial cancers are those which endometrioid type grade 3 stage Ib, clear cell carcinoma, serous carcinoma, and stages III and IV (1,5). In addition, women who are diagnosed with epithelial ovarian cancer (EOC) can suffer endometrial premalignancies, and women with endometriosis have risk to endometrial cancer, whereas the Natural Kill (NK) cell is lower (6,7). Moreover, vascular endothelial growth factor (VEGF) is angiogenic factor which plays important roles in the growth of endometrial cancers (8).

Hysterectomy with bilateral salpingo-oophorectomy is a treatment of choice, and adjuvant radiotherapy probably has benefit (9). Generally, endometrial cancer is radiosensitive. Adjuvant radiotherapy is previously said that may improve survival rate of high-risk endometrial cancer and decrease recurrences rate. Previously known prognostic factors of endometrial cancer are stage, age, histologic type, grade, invasion, and lympho-vascular space invasion (LVSI) (10,11). Radiotherapy may also make adverse effects. Diarrhea, urine retention due to urethra stricture, and fecal incontinencia are some of adverse effects post-radiotherapy of gynecologic cancer (12).

One problem which is frequently found in dr. Soetomo General Hospital, Surabaya is long queues. A previous research was explained that the interval time between post-operation to radiotherapy could affect outcome and cancer progressivity (13). Until this article written, there are no data

of outcome of post-radiotherapy high-risk endometrial cancer in dr. Soetomo Hospital for evaluation. Besides, there was affective psychopathological comorbidities affecting on the quality of life of patients who are undergoing radiotherapy (14). The aim of this study was to evaluate overall survival, disease-free survival in high risk endometrial cancer, and postradiotherapy side effects.

METHODS

This was an analytic retrospective study using medical record of post-radiotherapy high-risk endometrial cancer patients who underwent radiotherapy in dr. Soetomo General Hospital, Surabaya. The inclusion criteria in this study were high-risk endometrial cancer and having been done radiotherapy. Whereas, the exclusion criteria were incomplete required data, incomplete radiotherapy, and suffering from another cancer. The outcomes of this study were overall survival, disease-free survival, and adverse effects of radiotherapy. Variables of prognostic factors which were also evaluated are age, body mass index (BMI), parity, histopathology, stage, LVSI, history of lymphadenectomy, interval time, recurrences, and radiotherapy modality. Survival analysis was done using Kaplan-Meier. Log-rank test was performed for univariate analysis, cox regression was performed to evaluate time-dependent correlation among variables, and logistic regression was performed to evaluate correlation among variables without any specific time.

RESULTS

Characteristics

Medical record that had been done found 185 medical record of endometrial cancer patients who underwent radiotherapy in dr. Soetomo Hospital, Surabaya during period of 2013-

2018. Inclusion criteria were applied, and 77 patients met the criteria. Classification of characteristics was done according to some parameters as seen in Table 1. Most frequent use of radiotherapy modality in this study was combination of EBRT and brachytherapy. In this study, three patients were performed primary radiotherapy due to medically unfit for surgery. Radiotherapy modality for those three patients was EBRT only. One patient in this study performed only brachytherapy due to vaginal metastasis (stage III B).

Table 1: Patient characteristics

Characteristics	n	%	Mean ± SD / Median (min-max)
Age (years)			57.56 ± 8.19
<60	41	53.2	
≥60	36	46.7	
Body Mass Index (kg/m ²)			24.7 ± 5.5
<30	64	83.1	
≥30	13	16.8	
Parity			2 (0-9)
Nuliparity	16	20.7	
Multiparity	61	79.3	
Menopausal state			
Menopause	72	93.5	
Not menopause	5	6.5	
Histologic type			
Endometrioid	64	83.1	
Serous carcinoma	5	6.4	
Clear cell carcinoma	8	10.3	

LVSI		
Positive	34	44.1
Negative	43	55.9
Lymphadenectomy		
Yes	30	38.9
No	44	61.1
Radiotherapy modality		
EBRT	27	35.1
Brachytherapy	1	1.2
EBRT + Brachytherapy	49	63.7
Radiotherapy		
Adjuvant	74	96
Primary	3	4
IVA	1	
IVB	2	
Pre-radiation chemotherapy		
Yes	40	52
No	37	48

Overall survival

Overall survival analysis was performed in every variable as shown in Table 2. This study found 29 patient passed away with median time of passed away of 11 (CI 95% 2-43) month. Median with 95% CI showed period of time in which 50% of patients passed away. For overall survival, variables which statistically significant were age, BMI, stage, LVSI, queueing duration, and history of recurrence. Overall survival in age group of ≥60 was 61%, and DFS-3 years was 82% (p < 0.05). Obese patients significantly had better overall survival than

Table 2: All variable results

Characteristics	Alive (48) n (%)	Died (29) n (%)	OS (%)	OR	p	DFS-3 years (%)	p
Age (years)							
<60	23 (56.3)	18 (43.7)	39		0.04*	78	0.03**
≥60	25 (69.4)	11 (30.6)	61			82	
BMI (kg/m ²)							
<30	39 (60.9)	25 (39.1)	43		0.02*	72	NS
≥30	11 (84.6)	2 (15.4)	77			100	
Parity							
Nuliparity	11 (68.7)	5 (31.3)	58		NS	96	NS
Multiparity	37 (60.6)	24 (39.4)	46			88	
Menopausal status							
Menopause	46 (63.8)	26 (36.2)	48		NS	78	NS
Not menopause	2 (40)	3 (60)	80			100	
Histopathology							
Endometrioid	39 (60.9)	25 (39.1)	63		NS	78	NS
Serous carcinoma	2 (40)	3 (60)	76			90	
Clear cell	7 (87)	1(13)					
LVSI							
Positive	23 (67.6)	11 (32.4)	0	0.3 (0.1-0.8)	0.02**	50	0.004**
Negative	25 (58.1)	18 (41.9)	68			95	
Lymphadenectomy							
Yes	17 (58.6)	12 (41.4)	58		NS	84	NS
No	28 (62.2)	17 (37.8)	44			79	

Stage Early							
IA	2 (66.6)	1 (33.4)	78			87	
IB	22 (84.6)	4 (15.4)					
Advance							
II	4 (57.1)	3 (42.9)	37		0.002***	76	NS
IIIA	11 (64.7)	6 (35.3)					
IIIB	4 (80)	1 (20)					
IIIC	3 (50)	3 (50)					
IVA	1 (50)	1 (50)					
IVB	1 (9)	10 (91)					
Radiotherapy modality							
EBRT	16 (59.2)	11 (40.3)	43		NS	64	NS
Brachytherapy	1	0	-			82	
EBRT + Brachy	31 (63.2)	18 (36.8)	53				
Pre-rad. chemotherapy							
Yes	22 (55)	18 (45)	55		NS	78	NS
No	26 (70.2)	11 (29.8)	48			76	
Waiting time (weeks)							
<9	14 (45.1)	17 (54.9)	62	3.2 (1.1-8.8)	0.03**	91	0.007**
>9	34 (73.9)	12 (26.1)	35			76	0.013*
Recurrences							
Positive	4 (36.3)	7 (63.6)	0		0.014***		
Negative	44 (66.6)	22 (33.4)	22				

*cox regression; **logistic regression; ***log-rank

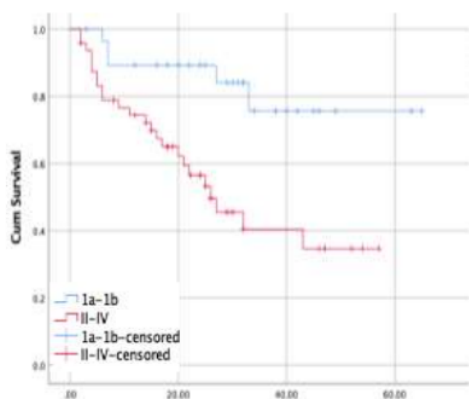


Figure 1: Kaplan-Meier curve for stadium

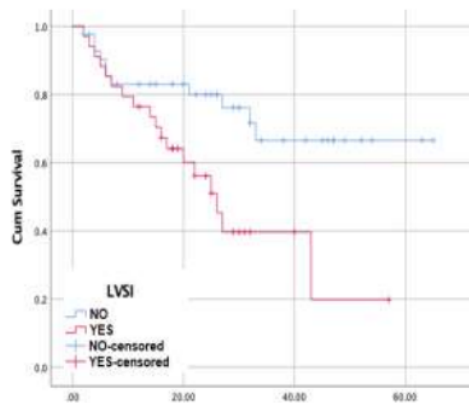


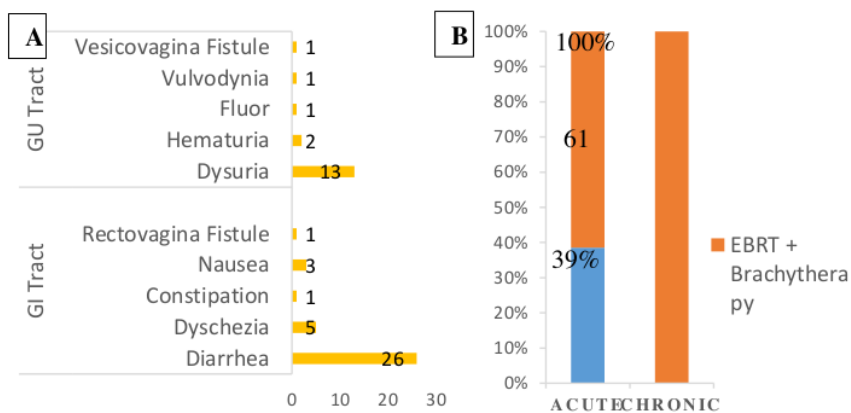
Figure 2: Kaplan-Meier curve for LVSI.



Figure 3: Metastasis distribution

Table 4: Effect of radiotherapy modality on adverse effect

Modality	Adverse effect			No adverse effect	p
	GI tract	GU tract	Both		
EBRT (n= 27)	12	3	3	9	NS
EBRT + Brachytherapy (n=49)	15	7	6	21	
Brachytherapy (n=1)	0	0	0	1	



EBRT = External Beam Radiotherapy; GI = gastrointestinal; GU = genitourinary; NS = Not significant

Figure 3: A. Symptoms distribution of GI tract and GU tract; B. Modality percentage to onset of adverse effect.

non-obese group (77% vs 43%). This study found 44.1% cases with LVSI positive. In group of LVSI positive, the OS was 0%, and logistic regression test found $p = 0.02$ with OR of 0.3 (CI 95% 0.1-0.8). Significant result of logistic regression test was also found in DFS-3 years with p value of 0.004. Stage classification was divided into early stage and advanced stage, and had significant different for OS of 78% vs 37%. In identifying the metastasis distribution, grouping of data according to metastasis location was performed as seen on Figure 3. Nine weeks of waiting time in this study was taken from the previous study which stated that nine weeks of waiting time could affect outcome of high risk endometrial cancer. In this study, group of patients whose waiting time for radiotherapy >9 weeks significantly had worse OS and DFS-3 years, 35% and 76%, respectively. From logistic regression test, the OR for OS was 3.2 (CI 95% 1.1-8.8) with p value of 0.03. Recurrences occurred 14.3%. In survival analysis test, patients with recurrence history had OS 0% with log-rank test p value = 0.001.

Adverse Effect

Radiotherapy also could cause adverse effects as summarized in Table 4. This study performed analysis of radiotherapy modality roles to adverse effect event. The adverse effects were classified to gastrointestinal and genitourinary tract, also acute and chronic effect. In Figure 3A, diarrhea and dysuria are the most frequent symptoms. Adverse effects occurred in combination modality of 61% as shown in Figure 3B. The statistical analysis of modality to adverse effect and onset of adverse effect showed no significant result.

DISCUSSION

Overall survival and DFS-3 years of patients with positive LVSI prognostic factors were lower than negative LVSI. Overall survival and DFS-3 years with prognostic factors of age ≥ 60 years and BMI >30 kg/m² were better than age <60 years and BMI <30 kg/m². Overall survival and DFS-3 years in the queuing group >9 weeks were lower than <9 weeks. Combination of radiotherapy modalities more often caused side effects than the external radiation group alone.

OS and DFS-3 years

Age is one of the prognostic factors that can determine whether or not adjuvant radiotherapy is needed. The results of this study indicated that OS in the <60 years age group was significantly lower than the >60 years age group, and the DFS-3 year rate was significantly lower than the ≥ 60 years group of 78% vs 82%. The results of this study were different from the results of other studies in general. Findings that might influence the results of the age group analysis in this study might be due to deep invasion (>50%) occurring more in the <60 years age group (37 vs 29). Determination of the role of age as a prognostic factor is still different among researchers. Most researchers stated that the older the age, the worse the patient's prognosis, however there is no agreed consensus (15,16). A 12-year cohort study said that age was not a prognostic factor in endometrial cancer (17). Another study said that no significant relationship was found for the

effect of age on the incidence of recurrence in grade 3 endometrial cancer (18).

Obesity is a risk factor for endometrial cancer, especially the endometrioid type, which is estrogen dependent. The relationship between IMT and OS is still controversial. Some studies say that increasing body mass index actually improves overall survival. This study significantly showed that the BMI group ≥ 30 kg/m² had better survival outcomes. Other studies mention similar results (19,20). The effect of BMI in this study might also be influenced by staging. In this study, all cases of stage IV A and IV B were in the BMI group < 30 kg/m², where 10 out of 11 cases of stage IVB died.

The histopathological type of endometrioid has a better prognosis than the non-endometrioid type. In this study, the type of histopathology did not have a significant relationship to overall survival. Differences in OS results with other studies may be caused by differences in staging at the time of therapy. For the endometrioid type, 11 cases of stage IVB were found in which 10 cases died. Whereas, for the type of clear cell carcinoma, of the eight cases of clear cell carcinoma, six cases constituted the initial stage (IA and IB), and two cases of stage III with only one patient's mortality.

The presence of LVSI is an important prognostic factor that can affect recurrence and OS. LVSI increases the risk of regional recurrence and metastasis compared to groups without LVSI for all grades, invasions and stages (21). This study showed the same results with other studies that OS in the positive LVSI group was lower than the negative LVSI group (22). The importance of LVSI is also shown by Uharcek's research which states that the effect of LVSI is not related to the depth of invasion or grade (23).

Determination of staging in endometrial cancer refers to the consensus of FIGO (2010). In this study, the early-stage group (IA-IB) had OS 78% better than the advanced-stage group (II-IV). These results were in accordance with recent studies (91% vs 52.2%) (24). Another study conducted in 2017 showed that the higher the stadium, the lower 5-year OS number regardless of histopathological type (25).

List of radiotherapy queues at dr. Soetomo Hospital is quite long even up to six months. The radiotherapy delay >9 weeks is a significant prognostic factor for recurrence and has a lower OS (13). The results of the analysis found that the queuing group <9 weeks had OS 62% better than the queuing group >9 weeks with OS 35%. In the logistic regression test, $p = 0.03$ was obtained with an OR of 3.2 (95% CI 1.1-8.8). These results were in line with previous report where in a group of patients with queues >9 weeks had a 2.07-fold risk of mortality (13). Queues have also been shown to significantly affect DFS-3 years and therapeutic response. The most frequent cause of long queues in dr. Soetomo Hospital is because the number of patients is not proportional to the number of radiotherapy tools and reasons for improving general conditions, other reason is not well documented in the medical record. The reasons for improving general conditions and logistical reasons are the most common reasons encountered (13). Delayed therapy in endometrial cancer can affect the proliferation and doubling time of endometrial cancer cells. Doubling time in endometrial studies has been investigated and the results of

the study showed that within 120 hours, the endometrial cancer cell proliferation index was three times (26). In this study, recurrence cases occurred in 11 cases (14.2%), and the results of statistical tests showed significantly lower OS than the group without recurrence. The majority of cases in this study was case of endometrioid type with grade 3 histopathology type. The results of this study were in accordance with other reports which stated the recurrence rates in grade 3 endometrioid were 19.6 %, 23.6% and 13.7%, respectively (18).

Adverse Effect

In this study, the majority of side effects occurred due to the combined modality of external radiation and brachytherapy (61% vs 39%). Besides, the combination modality in this study was a cause of chronic intoxication in the gastrointestinal tract and genitourinaria, but the results of statistical tests did not show significant differences. These results were in accordance with another study which compared the side effects of combination modalities (external radiation + brachytherapy) and brachytherapy alone. The results of the study showed that groups with combined modalities had higher incidence of side effects and mortality than brachytherapy alone (27).

The location of the uterus is close to the gastrointestinal tract and the genitourinary tract, so that adverse events are more common in these two organ systems. In this study, the most common side effect of the gastrointestinal tract was diarrhea, similar to the results of a study from Post Operative Radiation Therapy in Endometrial Cancer-1 (PORTEC-3) which mentioned 21% of diarrhea side effects (28). The occurrence of intoxication in the gastrointestinal tract may be explained by the fact that after intestinal mastectomy fill the empty space previously filled with the uterus, so more areas are affected by external radiation and also closer to the brachytherapy applicator (29). The most common complaint of genitourinaria after radiotherapy was pain during urination (dysuria). These results were consistent with Bradley and McHaffie's research which stated that post-radiotherapy cystitis is a common complication with complaints of dysuria, frequency, urgency, and nocturia (30). Basically, the bladder can tolerate adjuvant doses which are commonly used in radiotherapy better than the intestine (45-50 Gy). Five-year observations made by PORTEC-1 which evaluated the effects of adjuvant radiotherapy on endometrial cancer at doses up to 46 Gy showed that no serious side effects were found in the genitourinary system (30). Two cases of fistula were found in this study, vesicovagina fistula and rectovagina fistulae. Cases of post-radiotherapy rectovagina and vesicovagina fistulae are rare, but are serious complications. Some cases of fistulae occur due to the administration of high doses to control cases of vaginal metastases or adjacent organs (31). In the case of fistulas with vaginal necrosis, hyperbaric oxygen and pentoxifiline therapy can be performed (30). Pentoxifiline is a blood-flowing agent, can increase the number of erythrocytes, and increases the flexibility of leukocytes (32).

This study has limitations due to a retrospective study where it cannot control confounding or biased variables, but as in survival research in the field of oncology in general,

evaluating the success of therapy for a very long time makes it difficult for researchers to conduct prospective research and is also has ethical clearance issue.

CONCLUSION

Overall survival and DFS-3 years of patients with positive LVSI prognostic factors were lower than negative LVSI. Overall survival and DFS-3 years with prognostic factors of age ≥ 60 years and BMI >30 kg/m² were better than age <60 years and BMI <30 kg/m². Overall survival and DFS-3 years in the queuing group >9 weeks was lower than <9 weeks. Combination of radiotherapy modalities more often causes side effects than the external radiation group alone.

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