Association between timing of post-operative radiotherapy and recurrence in patients with endometrial carcinoma, Mansoura University experience.

Abozeed WN[1], Zahi MS[2], Attia SE[3]

[1] Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt.

Correspondence should be addressed to Waleed N. Abozeed, Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt, waleedabozeed@yahho.com.

Abstract

Introduction: Endometrial cancer is the most common gynecological tumor in developed countries, and its incidence is increasing. Adjuvant radiation therapy (RT) is an important line of treatment for this disease with marked effect as regarding improvement of local control and survival. We analyzed the impact of delay between surgery and RT initiation in patients with endometrial carcinoma.

Patient and methods: 256 patients with endometrial carcinoma who received adjuvant RT after hysterectomy from Jan 2012 and Dec 2014 were included in the study. All patients operated by hysterectomy, oophorectomy, and pelvic and par-aortic lymph node evaluation. The time interval between hysterectomy and the start of RT was calculated and according to that, patients divided in 2 groups; group 1 who received RT before 8weeks and group 2 received RT after 8 weeks from surgery. The effects of time interval on recurrence-free survival (RFS) and overall survival (OAS) were calculated.

Results: At the end of the study and after mean over all time of follow up 64.55 +/- 17.76 months, 48 cases (18.8%) recorded to develop recurrent disease and 40 cases (15.6%) were died. The RT was delivered with brachytherapy alone in 64 cases (25%), pelvic RT alone in 133 cases (52%), or both 59 cases (23%). A total of 140 (54.7%) patients started their RT before 8 weeks after radical surgery (group 1) and 116 patients (45.4%) started 8 weeks after surgery (group 2). Tumor recurrence was significantly associated with treatment delay. 34 cases (29.3%) in group 2 developed tumor recurrence compared to only 14 cases (10%) in group 1. Only 11 patients (7.9%) of group 1 died compared to 29 patients (25%) in group 2. the median recurrence free survival time was 79.5 months in group 1 compared to 64.845 months in group 2. The median OAS for group 1 was 82.043 months compared to 70.509 months in group 2 with significant P-value in both. On multivariate analysis and besides the late starting of RTH, also grade III and stage III disease were found to be significant factors as independent predictors of mortality and recurrence.

Conclusions: Starting adjuvant RT after 8 weeks for cases with endometrial carcinoma is associated with worse survival endpoints.

Introduction:

Endometrial carcinoma is the 4th most common cancer in women and the 1st gynecological cancer, with a prevalence of 11.2 per 100000 women and amorality rate of 2.2 per 100000 patients [1].

Surgery is the primary treatment for endometrial cancer and may be enough for early stage disease, but in advanced stages, adjuvant treatment including radiotherapy, chemotherapy or combination of both may be needed [2]

Giving treatment to cancer patients at appropriate time is so important to prevent tumor progression. In a previous analysis of 10,953 patients, there were 319 patients with endometrial carcinoma who were already diagnosed but there was a delay in their referral to health care providers to start treatment for a period about 54 days [3].

The effectiveness of adjuvant radiation therapy (RT) in reducing the risk of recurrence after radical surgery for cases of endometrial carcinoma has confirmed by many broad randomized studies [4]

The time of adjuvant RT has been confirmed to affect loco-regional recurrence rates in many other malignancies like head and neck cancers [5]. However, this effect is not clear in cases of endometrial carcinoma after surgery due to lack of enough evidence. Ahmad et al. published a report concluded that adjuvant RT given 6 weeks after surgery was associated with reduced survival and increase the rate of local recurrence [6].

In this research, we aim to study the impact of delaying adjuvant RT after surgery on recurrence rate, DFS and OAS in women with endometrial carcinoma.

Patients and Methods:

Between Jan 2012 and Dec 2014, a retrospective study was conducted at clinical oncology and nuclear medicine department, faculty of medicine, Mansoura university hospital. 256 patients with endometrial carcinoma were included. All cases were underwent total abdominal hysterectomy, bilateral salpingo-ophorectomy, and pelvic node assessment. After surgery, all cases received adjuvant RTH. Exclusion criteria includes; preoperative radiation treatment or adjuvant chemotherapy. Cases with positive LNs who received adjuvant chemotherapy with RTH were excluded and we include only positive LNs cases who received adjuvant RTH alone without chemotherapy due to intolerability to chemotherapy either because of old age or co-morbid condition). The time interval between surgery and RT was recorded. Patients were assessed with clinical and radiological examinations every 3 to 6 months. Survival data were calculated. Adjuvant RT consisted of brachytherapy alone, pelvic RTH alone, or combination. For cases with FIGO stage 1A and low-grade tumor (grade 1 or 2) and in the presence of risk factors (age more than 60 or LVI), brachy therapy alone was the modality of choice. Brachy therapy is also indicated in cases with grade 3 disease. For stage 1B disease and grade 1, also brachy therapy is the modality of choice. For grade 2 disease, either brachy or EBRT was given and for grade 3, either of them or combination was given. For stage 2 or 3 disease, EBRT was given either alone or combined with brachy therapy. Recurrence-free survival (RFS) was calculated from the date of hysterectomy to time of disease recurrence or last follow up. Overall survivals (OS) were calculated from the date of hysterectomy to the date of death or last follow up. Patients was identified in 2 groups, group 1 (140 patients) received post-operative RTH before 8 weeks and group 2 (116 patients) received RTH after 8 weeks. The research aims to study the impact of delay starting of adjuvant RTH on recurrence rate, DFS and OAS. Patients' characteristics were compared between the two groups. Univariate and multivariate analyses were done to assess also the impact of other variables like, age, tumor grade, lower uterine segment involvement (LUSI), lymphovascular invasion (LVSI) and staging on survival end points.

Statistical analysis

Statistical Package of Social Science (SPSS) program for Windows (Standard version 21) were used for data analysis. The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test.

Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data and median (min-max) for non-normal data. The two groups were compared with Student *t* test.

Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves was determined by Log-Rank test. Significant variables entered into linear regression model using the statistical technique to predict the most significant determinants and to control for possible interactions and confounding effects.

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value). The results were considered significant when the $p \leq 0.05$. The smaller the p-value obtained, the more significant are the results.

Results:

256 patients received adjuvant RTH at clinical oncology and nuclear medicine department, Mansoura university hospital from Jan 2012 till Dec 2014. All cases were undergoing TAH + BSO +/- LN dissection. All cases did not receive pre-operative RTH or adjuvant CTH. The mean age for all cases was 62.53 years. Regarding pathological assessment; 80 cases was grade I, 107 cases were grade II and 69 cases were grade III. 123 cases were stage I, 84 cases were stage II and 49 cases were stage III. Lower segmental involvement was presented in 91 cases (35.5%) and lympho-vascular invasion was positive in 84 cases (32.8%). Lymph node dissection could be done in 133 cases (52%). According to modality of RTH given as adjuvant treatment; 133 cases (52%) received external beam pelvic RTH (74 cases in group 1 and 59 in group 2), 64 cases (25%) received vaginal brachytherapy alone (34 cases in group 1 and 30 in group 2). and 59 cases (23%) received combined modality (32 cases in group 1 and 27 in group 2). At the end of the study and after mean over all time of follow up 64.55 +/- 17.76 months, 48 cases (18.8%) recorded to develop recurrent disease and 40 cases (15.6%) were died. This date was shown in table 1.

According to the time interval between surgery and starting of adjuvant RT patients was identified in 2 groups; group 1 (140 patients) received RT before 8 weeks after surgery and group 2 (116 patients) received RT after 8 weeks from time of surgery. Both groups are matched as regards age, pathological features and modality of RTH given without significant difference. But when comparing both groups as regards recurrence rate and overall survival there were significant difference. In group 1, only 14 cases (10%) developed recurrence compared to 34 cases (29.3%) in group 2. At the end of the study, only 11 patients (7.9%) of group 1 died compared to 29 patients (25%) in group 2. P-value was ≤ 0.001* as shown in table 2.

When data was analyzed, there was a significant difference between the 2 groups as regards RFS, where the median recurrence free survival time was 79.5 months in group 1 compared to 64.845 months in group 2. Also, it was significantly different when comparing grade, I and II disease with grade III, stage I and II disease with stage III. It was also better in cases without involvement of LUS, cases with negative LVI and in cases underwent LN dissection with significant difference as shown in table 3.

Table (1): patient characteristics

	The studied group (n=256)
Age/ years	
Mean ± SD	62.53±4.92
Min-Max	50-71
Group (1)	140 (54.7%)
Group (2)	116 (45.3%)
Grade	
I	80 (31.2%)
II	107 (41.8%)
III	69 (27.0%)
Stage	
I	123 (48.0%)
II	84 (32.8%)
III	49 (19.1%)
Lower segment involvement	
Yes	91 (35.5%)
No	165 (64.5%)
Lymph. vas. invasion	
Yes	84 (32.8%)
No	172 (67.2%)
Lymph node dissection	
Yes	133 (52.0%)
No	123 (48.0%)
Type of RTH	
Pelvic RTH	133 (52.0%)
Brachytherapy	64 (25.0%)
Combined	59 (23.0%)
Recurrence	
Yes	48 (18.8%)
No	208 (81.2%)
Time to rec or last f.u by months Mean ± SD	61.28±22.98
Mortality	
Died	40 (15.6%)
Survived	216 (84.4%)
Overall time of follow up by months Mean ± SD	64.55±17.76

Considering the assessment of overall survival between the 2 groups, there was significant difference. The median OAS for group 1 was 82.043 months compared to 70.509 months in group 2 with significant P-value. Also the difference in OAS was significantly different in grade I and II disease compared to grade III, in stage I and II disease compared to stage III, in cases presented with negative LVI compared to positive cases and in cases operated with LN dissection as shown in table 4.

Table (2): study groups

	Group (1) no=140	Group (2) no=116	Test of significance (p value)
Age/ years			t=0.231
Mean ± SD	62.60±5.01	62.46±4.83	P=0.817
Grade			
I	44 (31.4%)	36 (31.0%)	$\chi2$ =0.183
II	57 (40.7%)	50 (43.1%)	P=0.912
III	39 (27.9%)	30 (25.9%)	
Stage			
I	65 (46.4%)	58 (50.0%)	$\chi2$ =0.568
II	46 (32.9%)	38 (32.8%)	P=0.753
III	29 (20.7%)	20 (17.2%)	
Lower segment involvement			
Yes	51 (36.4%)	40 (34.5%)	$\chi2$ =0.105
No	89 (63.6%)	76 (65.5%)	P=0.746
Lymph. vas. invasion			
Yes	47 (33.6%)	37 (31.9%)	$\chi2$ =0.081
No	93 (66.4%)	79 (68.1%)	P=0.776
Lymph node dissection			
Yes	73 (52.1%)	60 (51.7%)	$\chi2$ =0.004
No	67 (47.9%)	56 (48.3%)	P=0.947
Type of RTH			
Pelvic RTH	74 (52.9%)	59 (50.9%)	$\chi2$ =0.116
Brachytherapy	34 (24.3%)	30 (25.9%)	P=0.943
Combined	32 (22.9%)	27 (23.3%)	
Recurrence			
Yes	14 (10.0%)	34 (29.3%)	$\chi2$ =15.5
No	126 (90.0%)	82 (70.7%)	P≤0.001*
Time to rec or last f.u by months			t=4.15
Mean ± SD	66.54±16.95	54.93±27.37	P≤0.001*
Mortality			
Died	11 (7.9%)	29 (25.0%)	$\chi2$ =14.14
Survived	129 (92.1%)	87 (75.0%)	P≤0.001*
Overall time of follow up by months			t=4.07
Mean ± SD	68.55±12.29	59.73±21.78	P≤0.001*

$\chi2$: Chi square test, t: student t test, *significant p≤0.05

Table (3): Kaplan-Meier Disease free survival (Month)

	Disease free survival					
	Median Survival time	Std. Error	95% CI Lower	95% CI Upper	Log Rank test	P - value
Group 1	79.500	1.649	76.269	76.269	18.112	≤0.001*
Group 2	64.845	3.051	58.865	58.865		
Grade						
I & II	81.770	1.237	79.345	84.196	82.77	≤0.001*
III	48.246	4.128	40.155	56.338		
Stage						
I & II	80.778	1.299	78.232	83.323	108.747	≤0.001*
III	39.408	4.657	30.281	48.535		
LSI						
Yes	66.725	3.290	60.278	73.173	7.458	0.006*
No	76.242	1.890	72.538	79.946		
Lymph. vas. invasion						
Yes	60.298	3.674	53.096	53.096	27.114	≤0.001*
No	78.994	1.615	75.829	75.829		
Lymph node dissection						
Yes	80.752	1.598	77.620	83.884	23.069	≤0.001*
No	62.943	2.845	57.366	68.520		
DFS	72.859	1.712	69.503	76.216		

Log Rank (Mantel-Cox) was used, CI: confidence interval

Table (4): Kaplan-Meier overall survival (Month)

	OS					
	Median Survival time	Std. Error	95% CI		Log Rank test	P - value
			Lower	Upper		
Group 1	82.043	1.147	79.795	84.291	16.013	≤0.001*
Group 2	70.509	2.495	65.619	75.398		
Grade						
I & II	82.316	1.078	80.202	84.429	51.681	≤0.001*
III	61.333	3.381	54.707	67.960		
Stage						
I & II	82.155	1.034	80.129	84.181	81.613	≤0.001*
III	54.265	4.151	46.130	62.401		
LSI						
Yes	73.593	2.550	68.595	78.592	3.18	0.074
No	78.594	1.517	75.621	81.567		
Lymph. vas. invasion						
Yes	68.01	2.954	62.222	73.802	22.533	≤0.001*
No	81.116	1.256	78.654	83.579		
Lymph node dissection						
Yes	81.662	1.326	79.062	84.261	14.029	≤0.001*
No	70.065	2.228	65.698	74.432		
Overall OS	76.816	1.342	74.187	79.446		

Log Rank (Mantel-Cox) was used, CI: confidence interval

On multivariate analysis and besides the late starting of RT, grade III and stage III disease were found to be significant factors as independent predictors of mortality. While also late starting therapy, grade III and stage III disease, LVI and absence of LN dissection were found to be significant factors as independent predictors of recurrence as shown in tables 5 and 6.

Table (5): Multivariate regression analysis for independent predictors of mortality

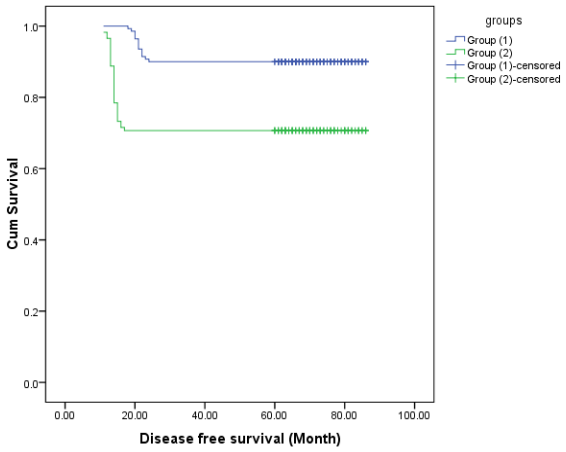
	B	SE	P value	OR	95 % CI
Grade					
I & II	2.45	0.395	≤0.001	1	(r)
III				6.22	2.5-15.5
Stage					
I & II	2.91	0.406	≤0.001	1	(r)
III				14.2	5.8-34
Lymph node dissection					
Yes	1.38	0.390	0.045	1	(r)
No				2.7	1.1-6
Type of RTH					
Pelvic RTH	2.54	0.419	≤0.001	12.7	5.6-29
Brachytherapy				Undefined	Undefined
Combined				1	(r)

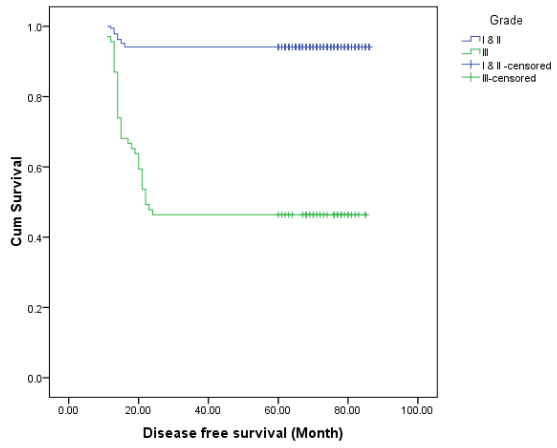
(r): Reference group, OR: odds ratio, CI: Confidence interval

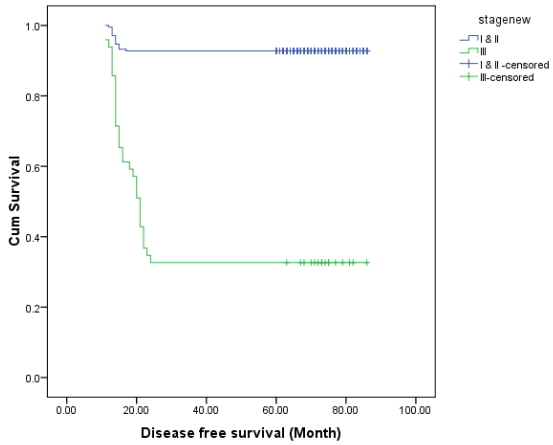
Table (6): Multivariate regression analysis for independent predictors of recurrence

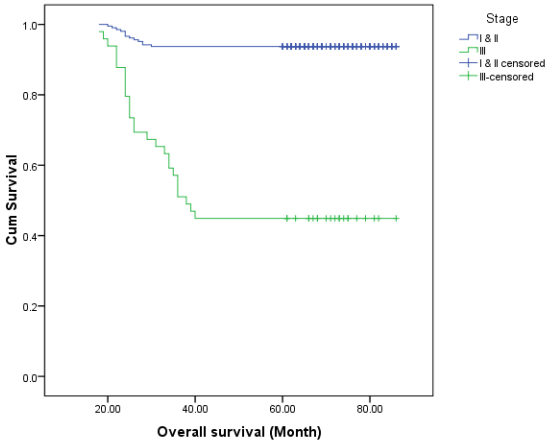
	B	SE	P value	OR	95 % CI
Grade					
I & II	3.054	0.615	≤0.001	1	(r)
III				21.2	6.3-70
Stage					
I & II	3.486	0.628	≤0.001	1	(r)
III				14.2	9.5-111
LSI					
Yes	0.785	0.341	0.021	2.2	1.1-4.3
No				1	(r)
Lymph. vas. invasion					
Yes	1.766	0.594	0.003*	5.8	1.8-18.7
No				1	(r)
Lymph node dissection					
Yes	1.672	0.386	≤0.001	1	(r)
No				5.3	2.5-11.3
Type of RTH					
Pelvic RTH	2.963	1.149	0.01	1	(r)
Brachytherapy				Undefined	Undefined
Combined				15.7	7.1-34

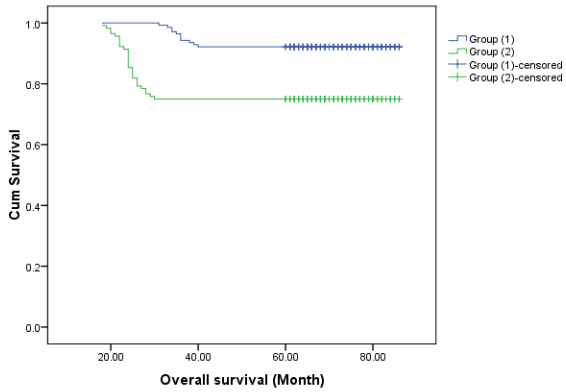
(r): Reference group, OR: odds ratio, CI: Confidence interval

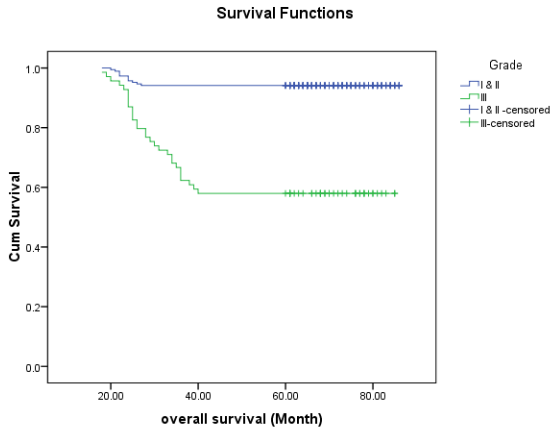












Discussion:

In this study we try to assess the effect of timing of starting radiotherapy after hysterectomy on disease control, DFS and OAS. Delaying RT after hysterectomy had a negative effect on RFS and OAS rates according to many studies [6&7]. It's worth noting that in Ahmad et al study [6], the assessed time between surgery and adjuvant RT was 6 weeks but the results were dramatically negative after 9 weeks. In our research, we compare between before and after 8 weeks from surgery with the same negative effect for delaying of RTH.

Fabrini et al [7] observed marked increase in local failure when adjuvant RT was delayed more than 9 weeks (8.1% vs. 0%) which similar to our results which was, In group 1, only 14 cases (10%) developed recurrence compared to 34 cases (29.3%) in group 2.

In a study done by Ghanem et al. they investigated the effect of waiting to start adjuvant radiotherapy on survival outcomes, using a cut-off of 8 weeks which is similar to our study [8]. They concluded that women treated before 8 weeks had improved OS as well as 10-year survival rates and that agree with our results. Using multivariate analysis, they confirm that many factors influenced the OS rates, but waiting interval was not between them that contrasts with our study which after multivariate analysis confirmed waiting interval as a strong factor influenced OS.

Luo et al. investigated the same point and used an interval cut-off of 1.6 months between hystrectomy and adjuvant RT to compare survival outcomes of endometrial cancer patients [9]. And like our study, they concluded that delay in treatment was associated with negative impact on OAS.

A single-institution study done by Cattaneo et al [10], they found that recurrence rates were higher when giving RTH after 9 weeks (90% vs. 39%, p=.001). Also, disease-specific and overall survival rates were lower (5.9% versus 33.3%, p.001, and 50% vs. 82%, p.001, respectively). All that results also matches with our results.

On the other hand, Martella and colleagues investigated only stage III endometrial cancer, and they used a cut-off period of 16 weeks to assess the effect of

delay in adjuvant treatment [11]. They found that the OAS did not affected by delaying in starting RTH. This result may be explained by the limited group included in the study (only stage III) which have poor outcome whatever time interval or modality used in treatment.

According to our study, and beside time interval before RT, Tumor grade and pathologic stage were also found to be independent prognostic predictors for recurrence and mortality in multivariate analysis. The same was found by Alvaro et al. [12] in which a retrospective study done on 276 patients with endometrial carcinoma. In the multivariate analysis, they found that advanced FIGO stage and high tumor grades are predictors of tumor recurrence. The same variables were also associated with a significantly higher risk of tumor-related mortality.

Lymph node dissection was done for 133 cases of our study group while 123 cases did not undergo any lymph node dissection during surgery. According to our results, lymph node dissection was associated with significant better RFS and OS. Also, in multivariate analysis, it was found to be a predictor factor for recurrence and mortality with significant P-value. Those results are comparable to the results of study done by Dogan et al [13]. They investigated 135 patients with clinically Stage I-II only endometrial carcinoma. Groupe 1 of those cases were underwent pelvic and paraaortic lymph node dissection during surgery. Groupe 2 did not undergo any lymph node dissection. Overall survival (OS) and recurrence-free survivals (RFS) were significantly better in group 1. And like our study, multivariate analysis confirmed that lymph node dissection was independent prognostic variable of OAS and RFS.

Conclusion:

More than 8 weeks delay in giving adjuvant radiation therapy after surgery in cases with endometrial carcinoma is associated with marked increase in recurrence rate and significant decrease in DFS and OAS. It is also recognized as strong predictor factor for recurrence and mortality beside high grade, advanced stage disease and lymph node dissection.

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