ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 23(3): 146-152, 2018
DOI: 10.5505/ejm.2018.96158

Evaluation of hematologic and biochemical parameters in patients with early stage uterine malignancy receiving radiotherapy

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ABSTRACT

Surgery is the primary choice of treatment for this disorder. Radiotherapy is an important step of treatment in this cancer after surgery due to the stage of the disease. Lack of prospective randomised data for survival limits the use of adjuvant radiotherapy. Hovewer adjuvant radiotherapy is suggested for high risk patients to reduce locoregional recurrence. The aim of this study is to define the statistical difference of hemogram, transaminases, kidney function tests and electrolyte changes in patients before starting radiotherapy, the end of radiotherapy, with the onset of acute side effects, and three months after finishing radiotherapy with the onset of chronic side effects.

18 patients with early stage endometrial malignancy attending to Adana Numune Training and Research Hospital have been included. This study has assessed the changes in hemogram, blood transaminases, urea, creatinin and electrolyte values of patients before radiotherapy, at the last week of radiotherapy and three months after radiotherapy.

The values were statistically significant for AST, Ca, LDH, urea, Hb and HTC values before treatment, at the end of the treatment and three months after treatment ($p<0.05$).

The effect of radiotheraphy seen as lower values of hemoglobin and hematocrite in endometrial malignancy patients resolved and become normal after three months of the radiotherapy.

Key Words: Endometrium cancer, Radiotheraphy, Hemogram

Introduction

Endometrium cancer is the most common gynecologic cancer in developed countries and worldwide. Endometrial cancer patients undergo primary surgical treatment with total hysterectomy, salpingo-oophorectomy, and lymphadenectomy in the presence of risk factors. Radiotherapy (RT) is considered as effective treatment modalities as adjuvant therapy for endometrial cancer. (1,2) If patients have high-risk features, such as, stage -IB, grade 3 cancer with deep myometrial invasion (Stage -2A), lymphovascular invasion, stage II or III cancer and non-endometrioid histology, have higher incidence of distant metastases and cancer-related death. Endometrium cancer displays favourable characteristics in some patients with long survival, however it is quite aggressive in others with metastasis in early stages. High risk patients with metastasis don't have long survival (3,4). According to the PORTEC-I study postoperative RT is given in Stage-1 endometrium cancer. Indication for external RT for Stage-1 endometrium cancer for local and regional control has been accepted after the study of gynecologic oncology group. In these studies old patients defined as high and medium risk, the increase in grade due to depth of invasion of pathologic myometrium, lenfovascular invasion and high grade are considered. PORTEC-I study recommended that pelvic RT significantly reduced loco-regional recurrence but not all-cause mortality (5,6). PORTEC-II study has assessed the effect of vaginal brachytherapy on local recurrence with external pelvic RT on high and intermediate risk patients who have undergone surgery. However; there was no significance between patients treated with only external RT and vaginal brachytherapy. PORTEC-2 trial showed that vaginal brachytherapy was effective as external RT because of reducing local recurrences in patients with early stage high-intermediate risk endometrial cancer. Adjuvant RT is recommended depending on risk features (only external RT and/or vaginal brachytherapy (7,8,9).

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Received: 27.12.2017, **Accepted:** 27.05.2018

Uterus sarcomas are seen less frequently than endometrial carcinomas. Uterus sarcomas resemble endometrium stroma with regard to histologic specialities. Uterus sarcomas constitute about 20% of endometrium cancers (10,11). Surgery is the primary choice of treatment for endometrium sarcomas and endometrioid type cancers of endometrium. Salpingo-oophorectomy and lymphadenectomy according to presence of risk factors are performed (12). Surgically removed material has great importance as it can guide with the stage of the disorder, prognosis, and whether additional treatment is needed and whether pathologic risk factors exist. Lack of data for prospective randomised survival limits the use of adjuvan RT. Adjuvant RT is suggested for high risk patients to reduce locoregional recurrence. Adjuvant RT does not effect the survival despite it manages local control. (13). RT is suggested if there are pathological lymph node invasion, if the tumor has high grade and if a defined residue mass exists. After patients are surgically stage, the role of adjuvant RT is an important step in the treatment of the disease. Therefore complications may develop or these complications may come up in the chronic period (14,15). The aim of this study is to define the statistical difference of hemogram, transaminases, kidney function tests and electrolyte changes in patients undergoing external radiotherapy by controlling at the beginning and at the third month of the treatment which corresponds to start of acute and chronic side effects of radiotherapy to check if these changes were associated to the start of acute and chronic side effects of radiotherapy.

Table 1. General descriptive data of the patients

	Mean ± SS
Age (year)	53.560 ± 9.605
Heigh +(cm)	162.940 ± 4.621
Weigh +(kg)	85.110 ± 9.003
	N (%)
Surgery type	
TAH+BSO	12 (66.6)
TAH+BSO+LND	6 (33.4)
Pathology	
Adenocarsinom	17 (94.5)
Leiomyosarcoma	1 (5.5)
Grade	
1	4 (22.2)
2	9 (27.7)
3	5 (50.1)
Stage	
1B	10(55.5)
2A	8(44.5)

Material and Method

18 patients with early stage endometrium cancer attending to Adana Numune Training and Research Hospital have been included in this study. The institutional ethic committee approved this study. Patients which were excluded, had hematologic, hepatic or renal diseases. Women with stage IB and 2A endometrial cancer who underwent hysterectomy were examined for postoperative RT. The patients demoghraphic data regarding age, height, weight, type of surgery, tumor histopathological type, stage, grade, radiotheraphy dosage were retrieved from medical records. And also, the laboratory parameters including hemoglobin

(HB), hematocrite (HTC), blood biochemistry tests like aminotransferases, urea, creatinin, LDH, calcium levels were obtained from medical data cards and included in the statistical analysis. The radiotheraphy was divided into three categories as before radiotherapy (RT0), the end of radiotherapy (RT1), three months after finishing radiotherapy (RT2). The

hematologic and laboratory findings were compared in these three different period of radiotherapy treatment

Statistical Analysis: Descriptive statistics for studied variables (characteristics) were presented as mean, standard deviation, minimum and maximum values. Paired t test was used to compare periods (Before treatment, After treatment and 3rd month). For determination of linear relationships among the variables, Pearson correlation analysis was carried out. Statistical significance levels were considered as 5%. The SPSS (ver. 13) statistical program was used for all statistical computations

Results

General descriptive data of the patients are given in Table 1. Mean age of the patients was 53.56 ± 9.605 years, mean weight was 85.11 ± 9.003 kg and mean height was 162.940 ±4.621 cm. Twelve patiens who have undergone total abdominal hysterectomy with bilateral salpigo ooferectomy and six patients who have undergone TAH+BSO with lymph node dissection were included. Seventeen patients had primary endometrium adenocarcinoma and one had endometrium leiomyosarcoma. According to pathologic stage, 10 patients (55.5%) were classified as Stage 1B and 8 patients a Stage 2A. The staging is done according to Federation of Gynecology and Obstetrics (FIGO) 2009 Surgical Staging System for Endometrial Carcinoma. (12)

Pathologically 4 patients (22.2%) were classified as grade 1, 9 patients (50%) as grade 2 and 5 (27.7%) as grade 3 (Table 1). All of the patients included in this study had recieved external RT for early stage endometrium cancer. They were given external curative RT and not brachytherapy and chemotherapy. Patients recieved 45-50.4 Gy lntensity Modulated RT (IMRT) planing RT as pelvic external curative dose (Table 2).

Table 2. Patients Radiotherapy dose

RT Dose	N (%)
45 Gy	12 (66.6)
50.4 Gy	6(33.4)

Four patients (22,2%) developed grade 1 diarrhea at the last week of radiotherapy, no other gastrointestinal complication was seen. Patients were aged between 38-72 years and were checked for hemogram, AST, ALT, LDH, Urea, Creatinin, Ca, CL to see if any changes for these values that correspond to before radiotherapy (RT0), the end of radiotherapy (RT1), three months after finishing radiotherapy (RT2) occured.

11 patients (66,1%) were classified as medium anemia with hemoglobin (Hb) values 10-11.9 g/dL and 5 patients (22,8%) as severe anemia with Hb values 8.0-9.9 g/dL. One patient had blood transfusion before RT who had RT0 Hb level of 8.7 gr/dL. Patients with Hb values 10,801 ± 1,795 at RT0 dropped down to 9,917± 1,083 at RT1. During the treatment patients were given care not to have their Hb values below 10g/dL. Five patients underwent blood transfusion as their Hb levels fell below 10g/dl at the last week of RT. Other patients displayed no signs of haematologic complications. AST, ALT, Ca, Creatinin, LDH, Urea RT1 showed a trend toward decreasing; AST, ALT, Creatinin, Urea RT2 toward increasing. Basophil count tend to increase in RT1 and to decrease in RT2. Results of analysis to define association between RT0-RT1 and RT2 are given in table 4.

RT0-RT2 differences for AST value was statistically significant p=0.004. RT1-RT2 differences for AST value was statistically significant p=0.002. RT0-RT2 and RT1-RT2 differences LDH value were statistically significant p=0.001. RT0-RT2 and RT1-RT2 differences for Urea value were statistically significant $p<0.05$. RT0-RT2 and RT1-RT2 differences for Hb and hemotocrit (HTC) were statistically significant ($p< 0.01$).

There was negative corelation between Htc and urea (r= -0,469) at RT0 and a negative corelation between Hb and basophil and (r=-0,47) at RT1. On the other hand there was a positive corelation between age and HTC at RT2 (49,2)%.

Discussion

Primary choice of treatment for endometrium cancer is surgery. Adenocarsinom is the most common seen pathology (table1). External curative RT is given in early stage endomtrium cancer according to pathologic risk factors (table 2). RT has acute and chronic effects. Acute side effects occur in cells which undergo rapid mitosis (gastrointestinal system, bone marrow, skin, oropharengeal and eusophagus mucosa). The severity of the side effects due to RT is associated with the technique of radiotherapy, total dose of RT, fraxination specialities and the width of the treatment site (16). Newman et al. have reported

Table 3. General defining statistics for RT0, RT1 and RT2

n =18	Before radiotherapy (RT0)			Last week of radiotherapy (RT1)			Three months after radiotherapy (RT2)		
	Mean ± SS	Min.	Max.	Mean ± SS	Min.	Max.	Mean ± SS	Min.	Max.
AST	21,060 ± 8,537	11	32	18,923 ± 10,233	2	38	28,063 ± 5,975	15	36
ALT	22,830 ±12,766	8	49	21,941 ± 11,196	8	46	29,061 ± 6,557	15	35
Ca	8,988 ± 0,629	7,90	10,00	8,961 ±0,876	7,20	10,10	8,462 ± 0,614	7	9
Cl	104,061 ± 5,662	95	115	104,616±6,185	96	121	102,001 ± 7,162	93	115
Creatinin	1,981 ± 4,610	,53	20,30	0,999 ± 0,867	0,1	2,9	1,029 ± 0,881	0,1	2,9
LDH	212,892 ±59,457	146	417	196,891 ± 33,228	148	268	123,224 ±43,729	67	200
Urea	6,238 ± 1,602	3,62	9,66	3,941 ± 1,436	2,34	6,50	6,127 ± 1,945	2,00	9,66
HB	10,801 ± 1,795	8,7	14,6	9,917 ± 1,083	8,0	11,8	12,483 ± 0,747	12	15
HTC	33,223 ± 4,826	25	43	32,867 ± 3,961	27,2	41,2	45,242 ± 6,091	38	43
BASO	0,026 ± 0,015	0,01	0,06	0,041 ± 0,048	0,01	,20	0,035 ± 0,028	0,01	,10

Table 4. Defining statistics of the differences and comparison results

	RT0- RT1		RT0- RT2		RT1- RT2	
	Mean ± SS	p	Mean ± SS	p	Mean ± SS	p
AST	2,139 ±7,000	,212	-7,000 ± 8,838	,004	-9,139 ± 10,610	,002
ALT	0,889 ± 6,286	,556	-6,222 ± 16,330	,124	-7,111 ± 15,370	,066
Ca	0,029 ± 1,270	,925	0,500 ± 0,777	,017	0,449 ± 0,634	,034
Cl	-0,556 ± 6,776	,732	2,056 ± 6,769	,215	2,611 ± 7,531	,160
Creatinin	0,981 ± 4,194	,335	1,027 ± 4,318	,341	0,024 ± 0,075	,216
LDH	16,000 ± 56,353	,245	89,667 ± 71,322	,001	73,667 ± 38,413	,001
Urea	3,032 ± 7,477	,114	7,097 ± 7,809	,002	4,150 ± 6,417	,014
Hb	0,883 ± 2,070	,088	-1,678 ± 1,649	,001	-2,561 ± 1,672	,001
HTC	0,357 ± 3,707	,687	-12,020 ± 8,104	,001	-12,378 ± 8,115	,001
BASO	-0,015 ± 0,050	,222	-0,009 ± 0,001	,491	0,006 ± 0,043	,594

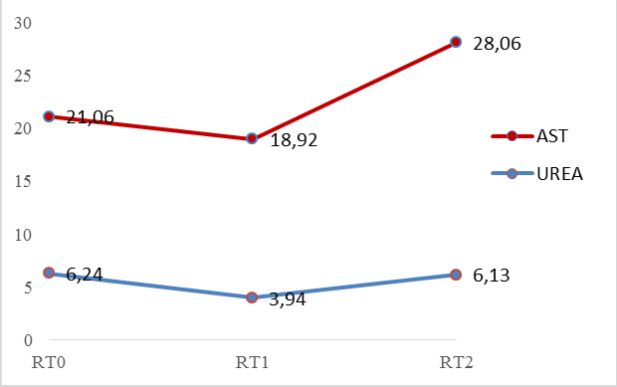
Table 5. Coefficients of corelation between Hb-Htc and other parameters

		Age	Heigh	Weigh	AST	CA	ALT	Cl	CREA	LDH	URE	BASO
RT0	Hb	,279	-,007	-,111	-,390	,285	,057	,019	-,342	,183	-,428	,425
	HTC	,220	-,163	-,138	-,444	,340	,039	-,139	-,378	,143	-,469*	,363
RT1	Hb	,364	,132	,132	,437	,208	-,406	,014	-,006	-,413	-,413	-,470*
	HTC	,379	-,006	-,006	,017	,175	-,230	-,140	-,208	-,085	-,085	-,260
RT2	Hb	,032	-,125	-,098	-,373	-,274	,204	-,093	-,269	,087	-,261	,336
	HTC	,492*	,378	-,391	-,134	-,054	-,218	,249	-,480	-,142	-,070	,194

*: $p<0.05$

relieved with symptomatic treatment six months after the end of RT in women. These side effects respond rapidly to semptomatic treatment and vanish in six weeks (17). Anemia is variable in 30-40% of cancer patients due to the primary site. Gynaecologic malignancies are frequently seen among cancer patients. Degree of anemia varies by the type of the gynaecologic tumor, the stage of the disease and treatment modalities. Prevelance of anemia is high in endometrial cancer (%72.2). Anemia in cancer patients has multiple reasons. Barrett-Lee et al. have reported that it is prognostically important in cancer patients that tumor cell causes hypoxia. Anemia causes microvascularization around the tumor cell and hypoxia therefore increases tumorogenesis (18). Vaupel P et al. have reported that the proliferation of cancer cells in a hypoxic mileu is a reason for radioresistance. The hypoxic mileu has prognostic importance for survival. (19) Non anemic cancer patients give good response to adjuvan RT and

Fig. 1. Changes in AST and Urea at RT0, RT1 and RT2



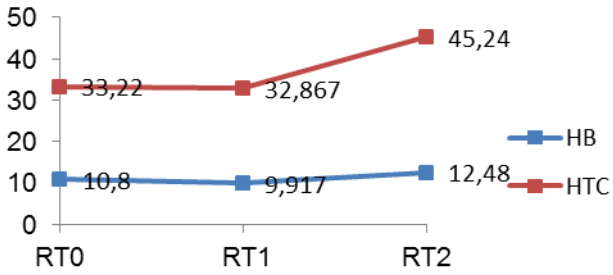
At RT1; AST and Urea values decrease, at RT2 AST ve Urea values increase

chemotherapy as a result of sufficient oxygenation. Non anemic patients respond better to treatment than anemic patients. The abscence of hypoxic milieu caused by tumorogenesis and sufficent oxygenation is important for response to treatment. RT response decreases for gynecologic tumors in patients with anemia therefore Hb levels must be monitorized to be over 10 gr /dl during treatment. In order the provide maximum RT effect patients with endometrium cancer must not have hypoxic mileu. Therefore Hb levels of these patients must be monitorized and closely followed (20). In our study patients who had Hb levels below 10gr /dl were given blood transfusion before RT.

Changes in hemogram, blood transaminases, urea, creatinin and electrolytes of patients at RT0 is given in table 3. Changes in AST, LDH, urea, Hb, HTC were statistically significant for RT0-RT1 $p<0.05$. Changes in AST, LDH, urea, Ca, Hb, HTC were statistically significant for RT1-RT2 $p<0.05$ (table 4). Changes in basal values of AST, Urea (Figure 1). ALT, Ca, CL, creatinin, LDH, RT0 was significant for RT1 and RT2 but nevertheless meaningless clinically.

Hb and Htc values of patients receiving RT may decrease due to supression of blood marrow (14). In our study Hb and Htc values of patients was below RT0 measurements and were statistically significant $p=0.01$. The values which showed a decline trend in RT 1 show increase in RT2 with statistical significance. $p=0.01$ (tablo 4, Figure 2). In this study the Hb levels of patients which drop down at RT1 reach back to 12,483 ± 0,747 (normal level) at RT2. The change in HTC value was similar. HTC was 33,223 ± 4,826 at RT0, 32,867 ± 3,961 at RT1 and 45,242 ± 6,091at RT2. In this study the Hb levels of patients which drop down at RT1 reach back

Fig. 2. Changes in Hb and HTC at RT0, RT1 and RT2



At RT1; Hb and HTC values decrease, at RT2 Hb ve HTC values increase

to normal at RT2 (Figure 2). Anemia may develop in patients due to pelvic RT. However; these acute side effects resolve after RT. (21) Five patients went under blood transfusion as their Hb levels fell below 10g/dl at the last week of RT. Patients with medium anemia were not given symptomatic treatment. (22) F.A. Eggink et al. have classified endometrium cancer patients into two groups as low-medium risk and high risk. When adjuvant treatment was given in low-medium risk group complication rate was 85% and 61% for high risk group (23). In our study al the patients were low risk stage 1A and stage 2A patients. No complication to stop RT was seen. Agata Jodda et al. have compared different RT planning strategies of cervical and endometrial cancer. 50 patients have received RT in that study. Their major aim was to compare different bone marrow doses. The group that was given external RT with IMRT treatment plan required lesser bone marrow dose compared to the group that recieved RT as three dimensional conformal. (24) Our cases reieved IMRT treatment plan and no seriours fall in Hb and Htc levels at RT1 is seen. Vuthinun Achariyapota et al. have found an increase in anemia in patients with gynecologic cancer recieving adjuvan treatment. Anemia causes fatique symptoms (25). Cella et al. have shown that anemia decreased the quality of life in cancer patients as Demetri et al. (26,27) Dische et al. have found that adverse reactions due to anemia were common in patients recieving RT (28). Karsten et al. have shown that local control and survi decreased in patients who underwent RT and displayed decrease in Hb levels (29). Presence of positive correlation at RT2 between Hb and age was thought to be a reason of paliative support that was give to these patients (table 5). In our present study we have assessed the hemogram, transaminases, kidney function tests and electrolytes of patients at RT0, RT1 and RT2 and saw that Hb and Htc levels decreased in RT2 measurements. The group of patients was small but homogenous in terms of being early stage and

recieving external RT only, but the cases were not given chemothrapy or brachi therapy.

Anemia is frequently seen in cancer biology. It is also frequently seen in endometrium cancer of gynaecologic tumors. Hb and HTC values of patients recieving pelvic radiotherapy must be followed. In this study it was seen that the values which drop below normal levels reach back to normal after three months from cessation of radiotherapy. This study showed that basal values of Hb and Htc at RT0 declined in RT1 in patients recieving external pelvic radiotherapy. These values surpassed RT0 basal values at RT2. We believe our actual study has underlined the importance of monitorization of Hb and Htc levels in patients recieving pelvic RT.

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