Patterns of Disease Relapses in Patients with High-risk Endometrial Carcinoma Following Concurrent Chemoradiation with Paclitaxel

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Abstract

Background: Women with high-risk endometrial cancer have a relatively higher recurrence rates and poor prognosis following hysterectomy alone. Adjuvant radiotherapy and chemotherapy had been proposed to improve these outcomes. Patterns of relapse are influenced by adjuvant treatment received and other clinical and pathological factors.

Objectives: Analysis of patterns of relapse in patients with high-risk endometrial carcinoma after Concurrent chemoradiation (CCRT) versus radiotherapy alone (RTH).

Patients and methods: This is a randomized controlled trial (RCT) of patients with high risk endometrial carcinoma. Patients are divided into two arms: Arm A received weekly paclitaxel and pelvic radiotherapy, Arm B radiotherapy alone. During follow-up; disease relapses were recorded regarding time of failure, site of disease relapse and survivals data.

Results: Seventy-one patients were includedin the study; 34 patients received CCRT; and 37 patients received RTH alone. Thirteen patients [18.3%] had a treatment failure; treatment failures are more in RTH group, but without statistical significance [p-value =0.51]; 2 patients had loco-regional failure, 8 patients had distant metastases and 3 patients had both regional and distant failure.Estimated 2-years OS was around 86% with no statistical significance between both treatment arms [p-value = 0.83], and estimated 2-years DFS was; 83.2% for CCRT arm and 77.1% for RTH arm, with no statistical significance [p-value = 0.48].Other disease and treatment related factors didn't show statistical significance regarding disease relapses.

Conclusion: Adding concurrent paclitaxel to pelvic radiotherapy did not decrease disease relapse in high-risk endometrial cancers.

Keywords: Endometrial Carcinoma; Radiotherapy; Concurrent Chemotherapy.

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Introduction

Most patients with endometrial cancer generally have afavorable prognosis; only about 15–20% have high-riskdisease associated with an increased risk of pelvic recurrence and distant metastases that contribute to the inferior outcomes of this group(**Mundt et al., 2001).**

According to ESMO-ESGO-ESTRO consensus; includes any of the following features: stage IB, stage II – III, grade 3, positive lymph-vascular space invasion (LVSI), non-endometrioid histology(**Colombo et al., 2016**).

Following radical surgery, adjuvant pelvic radiotherapy is indicated for high-risk patients. Randomized trials tested adjuvant chemotherapy in this sitting also. Pelvic radiotherapy resulted in better pelvic control, while chemotherapy delayed distant failure. Concurrent chemoradiation (CCRT) rational depends on hypothesis that combined modality could result in better control at pelvis and distant sites(**Alvarezsecord et al., 2007**).

Two large randomized trials; PORTEC-3(**de Boer et al., 2018)** and GOG-258(**Matei et al., 2019);** tested CCRT versus radiotherapy alone and chemotherapy alone, respectively. Both trials showed trend to improved disease free survival, but not overall survival. Unfortunately, this came in expense of more adverse events(**de Boer et al., 2016**).

We conducted a prospective trial to evaluate benefit and toxicity of adding weekly paclitaxel concurrently with pelvic radiotherapy in adjuvant treatment in high-risk endometrial cancer patients, presented to South Egypt Cancer Institute, Assuit University. In this article, we report patterns of disease relapses and related factors.

Patients and Methods

During the period from October 2019 to June 2021, patients with high-risk endometrial cancer presented to Radiation Oncology Department, South Egypt Cancer Institute, Assuit University, for adjuvant therapies following surgical management were randomized to either concurrent chemotherapy with radiotherapy or radiotherapy alone.

Inclusion criteria: Patient with histologically confirmed endometrial carcinoma, who underwent total hysterectomy with bilateral salpingo-oophrectomy, with one of the following features: stage IB, stage II – III, grade 3, positive lymph-vascular space invasion (LVSI), non-endometrioid histology.

Exclusion Criteria: Patients with uterine leiomyosarcoma, previous pelvic radiotherapy, history of prior primary related tumors; like breast and ovarian cancers or metastatic disease after surgery, were excluded from the study.

Study design: Eligible patients were randomly assigned to one of the following arms: Arm A; were treated with radiotherapy, concurrently with weekly paclitaxel. While, patients in Arm B; were treated with radiotherapy alone.

Radiotherapy technique: The clinical target volume (CTV) consisted of the proximal 1/2 of the vagina, the parametrial tissues, and the internal, external and distal common iliac lymph node regions up to the upper S1 level. Total dose was 50.4 Gy, at 1.8 Gy per fraction, specified at the isocenter, 5 fractions a week. For all patients a CT-scan based three-dimensional treatment planning was used. A planned volume (four-field ‘box’, 3-field or multiple field techniques with or without supplementary fields or segments) was employed.

Patients with cervical stromal invasion, vaginal involvement or parametrial invasion

were referred to brachytherapy center for additional vaginal vault brachytherapy, after finishing external beam radiotherapy.

Chemotherapy: Patients in CCRT arm received paclitaxel (50 mg/m2), intravenously on a weekly basis (total 5 cycles), concurrently with radiotherapy. An adequate blood count was required in all patients before each cycle. Additional antiemetic or growth factors were given when indicated.

Follow-Up: Follow up visits were scheduled as follow; every 3 months in the 1st year, then every 6 months in the 2nd year, starting from 1st day of treatment.

For each visit patient were evaluated by; physical examination, complete pelvic examination, assessment of treatment related toxicity. Other imaging (including pelvic MRI) and investigations were requested as clinically indicated.

Ethical consideration: The current study has been approved by the Ethics Committee of South Egypt Cancer Institute, Assiut university, Assiut, Egypt.

Statistical Analysis

Per protocol analysis was done for patients completed planned treatment. Statistical analysis of data was done by the statistical package for the social science (SPSS) using Version 24. Descriptive statistics was used as median, mean, number and percentage. Kaplan-Meier test used for survival analysis, and Log rank test was used to evaluate the significant differences in survival of both groups. Chi-square test was used to evaluate the relation between groups and treatment toxicities. P value was double sided and considered significant if was ≤0.05.

Results

Seventy-one patients met the eligibility criteria; 34 patients received concurrent chemo-radiotherapy [Arm A; CCRT]; and 37 patients received radiotherapy alone [Arm B; RTH].Three patients were omitted from the study after receiving treatment in arm A; due to associated borderline cardiac disorders and refusal to continue treatment, and excluded from final analysis.

The median age at time of diagnosis is 66 years. Most of our patients were older than 60 years; 85.2% in CCRT arm, and 86.5% in RTH arm. Nearly half of our patients presented with stage II or III [53.5%]. Regarding histological diagnosis; 48 patients [67%] were endometrioid endometrial carcinoma [EEC] and 23 patients [32.4%] were with non-endometrioid histology. Lympho-vascular space invasion was present in 45 patients [63.4%].**Table (1)** summarized our patients and disease characteristics .

After median follow-up of 23 months; estimated 2-years OS was 87% versus 85% (p-value=0.83, **Figure 1**) and estimated 2-years DFS was 83% versus 77% (p-value=0.48, **Fig.2**) for CCRT arm versus RTH arm, respectively.

During follow-up, 13 (18.3%) patients showed a treatment failure; 2 patients with loco-regional failure, 8 patients with distant metastases and 3 patients with both regional and distant failure. Treatment failures are more in RTH group, but without statistical significance (p-value =0.51).**Table (2)** prescribes patterns of first relapse between treatment arms, and **Table (3)** summarizes clinical data in relapsed patients.

For 13 relapses in our sample, analysis of disease related factors e.g., stage, histological type and LVSI failed to show statistical dependence on these factors. Also, lymph node dissection, vaginal brachytherapy or additional chemotherapy didn't decrease rate of disease relapses significantly. **Table (4)** shows clinical and treatment related factors in relapse rates.

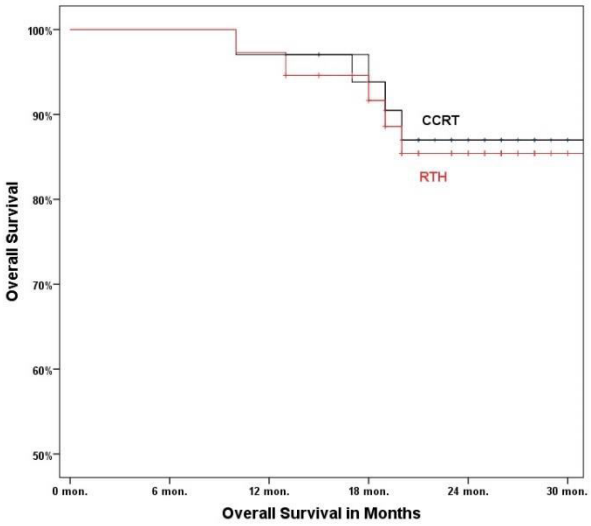

Fig.1. Overall survival

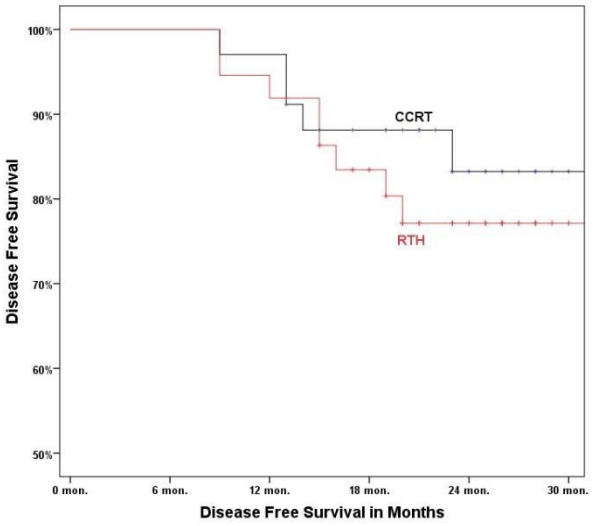

Fig.2. Disease-free survival

Table 1. Patients and Disease Characteristics

Variables	CCRT (n=34)	RTH (n=37)	All (n=71)	p-value
Age				**0.88**
Median (Range)	66 (52 – 75)	66 (53 – 77)	66 (52 – 77)	
<60 years No. (%)	5 (14.7%)	5 (13.5%)	10 (14.1%)	
≥60 years number (%)	29 (85.2%)	32 (86.5%)	61 (85.9%)	
ECOG Performance Status				**0.84**
0 No.(%)	12 (35.3%)	11 (29.7%)	23 (32.4%)	
1 number (%)	20 (58.8%)	23 (62.2%)	43 (60.6%)	
2 No. (%)	2 (5.9%)	3 (8.1%)	5 (7.0%)	
FIGO 2009 Staging				**0.92**
Stage Ib No. (%)	16 (47.1%)	17 (45.9%)	33 (46.5%)	
Stage II/III No. (%)	18 (52.9%)	20 (54.1%)	38 (53.5%)	
Histology and Grade				**0.99**
EEC G1 No. (%)	5 (14.7%)	5 (13.5%)	10 (14.1%)	

EEC G2 No. (%)	10 (29.4%)	11 (29.7%)	21 (29.6%)	
EEC G3 No. (%)	8 (23.5%)	9 (24.3%)	17 (23.9%)	
Non-ECC No.(%)	11 (32.3%)	12 (32.4%)	23 (32.4%)	
● Serous No. (%)	7 (20.6%)	7 (18.9%)	14 (19.7%)	
● Clear Cell No. (%)	4 (11.8%)	5 (13.5%)	9 (12.7%)	
LVSI				**0.82**
Yes No. (%)	22 (64.7%)	23 (62.2%)	45 (63.4%)	
No No.(%)	12 (35.3%)	14 (37.8%)	26 (36.6%)	

Table 2. Patterns of First Treatment Relapses

Variables	CCRT (n=34)	RTH (n=37)	All (n=71)	p-value
Treatment Failure No. (%)	5 (14.7%)	8 (21.6%)	13 (18.3%)	0.51
Loco-regional No. (%)	2 (5.9%)	2 (5.4%)	4 (5.6%)	0.64
Distant No. (%)	3 (8.8%)	6 (16.2%)	9 (12.7%)	0.32

Table (3) Sites and Time of Treatment Relapses

Patient	Stage at Diagnosis	Study Arm	Sites of Relapse	Time to Relapse (months)
1	IIIc	CCRT	Para-aortic LN, Peritoneum	23
2	IIIb	CCRT	Vaginal vault	13
3	Ib	CCRT	Pelvic LN, Peritoneum	20
4	IIIc	CCRT	Lungs, Liver	12
5	IIIc	CCRT	Para-aortic, Lungs	17
6	Ib	RTH	Peritoneum, Lungs	10
7	IIIc	RTH	Bone, Liver	19
8	IIIc	RTH	Liver, Peritoneum	15

9	IIIc	RTH	Pelvic LN, Liver, Peritoneum	14
10	II	RTH	Para-aortic LN, Lungs	9
11	IIIc	RTH	Liver	16
12	Ib	RTH	Pelvic LN	15
13	IIIb	RTH	Pelvic LN, Peritoneum	13

Discussion

Women with high-risk endometrial cancer have a relatively poor prognosis following hysterectomy alone. Therefore, adjuvant treatment is often administered. High-risk endometrial cancer is characterized by an increased risk of pelvic recurrence and distant metastases that contribute to the inferior outcomes of this group(**Mundt et al., 2001**).

For many years, pelvic radiotherapy has been standard adjuvant treatment for patients with high-risk endometrial cancer aiming to decrease pelvic recurrences. Randomized trials compared adjuvant chemotherapy to radiotherapy failed to show improvement in DFS and OS. Also, chemotherapy alone was associated with more pelvic relapses **(Susumu et al., 2008).** These observations led to a hypothesis of testing combined modality.

Table (4) Clinical and Treatment related Factors in Relapse Rates

Variables	Patients (number)	Relapses (number)	p-value
Whole Group	71	13	
Study Arm			0.51
● CCRT	34	5	
● RTH	37	8	
Age			0.77
● < 60 years	10	1	
● ≥ 60 years	61	12	
Stage			0.17
● Ib	33	3	
● II/III	38	10	
Histology			0.89
● EEC	48	9	
● Non-EEC	23	4	
LVSI			0.87
● Yes	45	8	
● NO	26	5	
LND			0.98
● Yes	49	9	
● No	22	4	
Brachytherapy			0.93
● Yes	32	6	
● No	39	7	
Additional Chemotherapy			0.75
● Yes	30	6	
● NO	41	7	

The phase 2 RTOG-9708 trial(**Greven et al., 2006**) studied combining cisplatin concurrently with pelvic radiotherapy in 46 patients. Marzi et al.(**De Marzi et al., 2010**) evaluated adding weekly paclitaxel to pelvic radiotherapy in 47 patients. Two large randomized trials tested concurrent chemoradiation either versus radiotherapy alone; PORTEC-3 trial(**de Boer et al., 2018**) (300 patients, stage I-III), or versus chemotherapy alone; GOG-258 trial(**Matei et al., 2019**) (370 patients, mainly stage III). In our study; we included 71 patients with high-risk endometrial cancer for evaluating the benefit of adding concurrent weekly paclitaxel

with adjuvant radiotherapy, versus radiotherapy alone.

Endometrial carcinoma mostly presented in post-menopausal women. The median age for our patient group was 66 years, with most patients older than 60 years [86%], which is comparable to data from Chapman et al. **(Chapman et al., 2019)** and Binder et al. **(Binder et al., 2017)** studied combined adjuvant chemoradiation in similar age group; median age was 62 and 66 years, respectively.

Regarding to tumor staging in our study; we included high-risk stages; as 47% were Stage Ib, and other patients were stage II or III. RTOG-9708 trial**(Greven et al., 2006)** and PORTEC-3 trial**(de Boer et al., 2018)** included patients with stage I as well as higher stages. In contrast to GOG-258 trial**(Matei et al., 2019)** and other reports focused only on stage III patients; as done by Binder et al. **(Binder et al., 2017)**, Cho et al. **(Cho et al., 2014)** and Chapman et al. **(Chapman et al., 2019)**.

After median follow-up of 23 months; the estimated 2-years overall survival [2-yr OS] in CCRT arm was 87% and 2-years disease free survival [2-yr DFS] was 83%. While in RTH arm 2-yr OS and DFS was 85% and 77%, respectively. No statistical difference between both arms in our study.

Survival rates in CCRT arm of our study were comparable to those reported in RTOG-9708 trial**(Greven et al., 2006)** [using cisplatin] and Marzi et al.**(De Marzi et al., 2010)** study [using paclitaxel]. Estimated 2-yr OS was 91% and 90% respectively, and estimated 2-yr DFS was 84% and 85% respectively.

In PORTEC-3 trial**(de Boer et al., 2018)**, DFS was statistical different between CCRT and RTH only arms, more evident in stage III patients. We couldn't find statistically significant difference between both arms outcomes. This could be contributed to small sample, shorted follow-up in our study.

The rate of relapses in our study was 5% and 13% for regional and distant sites, respectively. We couldn't detect statistical significance between treatment arms (p-value=0.51), and neither between different disease and related factors. Still, higher disease stage and presence of LVSI was associated with higher rates of relapse.

Hochreiter et al. **(Hochreiter et al., 2020)** reported a pelvic recurrence rate of 11% in patients treated with vaginal brachytherapy only. They concluded that lower uterine segment involvement and larger tumor size (>4cm) were factors for significant higher relapse rate. Also, grade 3 histology, presence of LVSI and deep myometrial invasion were associated with more regional relapses, but without statistical significance. They recommended for adding pelvic radiotherapy to patients with these risk factors.

In PORTEC-3 trial higher relapses occurred in patients with nodal disease (stage IIIc), presence of LVSI and deeper myometrial invasion. They reported distant failure risk of 21% and 27% for CCRT and RTH groups, respectively **(de Boer et al., 2019)**. While in GOG-258 trial; nodal relapse was 11% versus 20%, and distant metastasis was 27% versus 21% for CCRT arm versus chemotherapy arm, respectively**(Matei et al., 2019)**.

Different reports on rates and patterns of relapses after chemoradiation showed higher rates than our data. Gadducci et al.**(Gadducci et al., 2018)** reported distant relapses more than 30%, and regional relapses in about 5%. Cho et al.**(Cho et al., 2014)** studied adding paclitaxel to radiotherapy in stage III patients showed 34% of distant relapses and 2% for regional relapses. In our sample we had about 45% of stage Ib patients and patients with para-aortic LN was excluded, in contrast to these reports in which

patients were stage III or with positive para-aortic LNs were included.

Conclusion

Adding weekly paclitaxel regimen to adjuvant pelvic radiotherapy in patients with high-risk endometrial carcinoma did not decrease rates of both regional and distant relapses in these patients.

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