Concurrent Chemoradiation versus Radiotherapy Alone in Adjuvant Setting for High-Risk Endometrial Carcinoma

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Abstract:

Background: For endometrial carcinoma, the main surgical treatment is total hysterectomy and bilateral salpingo-oophorectomy. Women with high-risk endometrial cancer have a relatively higher recurrence rates and poor prognosis following hysterectomy alone. Therefore, pelvic external beam radiotherapy has been the standard adjuvant treatment for these patients. This is a prospective study on patients with high-risk endometrial cancer evaluating the benefit of adding concurrent weekly paclitaxel with adjuvant radiotherapy, versus radiotherapy alone.

Methods: Eligible patients were randomized to Arm A; Concurrent chemotherapy with radiotherapy [CCRT], and Arm B; External beam pelvic radiotherapy alone [RTH]. Pelvic radiotherapy was 50.4Gy over 28 fractions, and chemotherapy course was weekly paclitaxel (50mg/m2) for 5 weeks. Patients were evaluated for treatment related toxicities, disease failures and survival.

Results: Seventy-one patients met the eligibility criteria of study protocol; 34 patients received CCRT; and 37 patients received RTH alone. The median age at time of diagnosis is 66 years. Regarding to tumor staging; 47% were Stage Ib, and other patients were stage II or III. Grade 3 toxicity were more in CCRT arm, and no grade 4 toxicity were recorded. The most common events were diarrhea and hematological affection. No significant difference in acute toxicities between treatment groups; except for hematological affection with concurrent paclitaxel [p=0.025]. Ten patients [14%] had a treatment failure; treatment failures are more in RTH group, but without statistical significance [p-value =0.51]. 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].

Conclusion: Adding concurrent paclitaxel to pelvic radiotherapy in high-risk endometrial cancer patient is safe and tolerable, and tends to decrease treatment failures, even though this not translated to OS nor DFS improvement.

Keyword: Endometrial Carcinoma; Radiotherapy; Concurrent Chemotherapy

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Background:

Uterine cancer is the most common gynecologic malignancy in high-income countries and the second most common in low- and middle-income countries (cervical cancer is more common). Endometrial adenocarcinoma is the most common histologic site and type of uterine cancer.[1]

There are several histologic types of endometrial carcinoma. Endometrioid histology is the most common, and this typically presents at an early stage with abnormal uterine bleeding, and is most common in postmenopausal women. The non-endometrioid histologies: serous, clear cell, mixed cell, and undifferentiated may have more aggressive clinical behavior.[2]

The main surgical treatment is simple hysterectomy and bilateral salpingo- oophorectomy (BSO), peritoneal cytology, and some form of regional lymph node assessment.[3] For adjuvant treatment following surgery, treatment is stratified based on the risk of disease recurrence, which is characterized using the stage of disease (FIGO staging 2009), histology of the tumor, and other pathologic factors.[4]

According to ESMO-ESGO-ESTRO consensus; high-risk endometrial cancer represents stage IA with myometrial invasion, grade 3 with lymph-vascular space invasion (LVSI), stage IB grade 3, stage II – III

and stage IA with myometrial invasion, IB, II or III with serous or clear cell histology.[5] 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.[6]

Pelvic external beam radiotherapy has been the standard adjuvant treatment for women with high-risk endometrial cancer for many decades. Randomized trials have compared adjuvant chemotherapy with external beam radiotherapy. Radiotherapy was shown to delay pelvic recurrence and chemotherapy was shown to delay distant metastases, but no differences in survival were found.[7] Therefore, it was logical to hypothesize that an approach that combined the methods of treatment would improve outcomes by preventing local (pelvic) and distant recurrences.

RTOG-9708 trail studied combining cisplatin concurrently with pelvic radiotherapy, while Marzi et al. evaluated adding weekly paclitaxel to pelvic radiotherapy. Two large randomized trails tested concurrent chemoradiation either versus radiotherapy alone; PORTEC-3 trail, or versus chemotherapy alone; GOG-258 trail. [8-11]

This is a prospective study on patients with high-risk endometrial cancer evaluating the benefit of adding concurrent weekly paclitaxel with adjuvant radiotherapy, versus radiotherapy alone.

Patients and Methods:

This is a prospective study on patients with high-risk endometrial cancer presented to Radiation Oncology Department, South Egypt Cancer Institute, Assuit University, for adjuvant therapy following surgical management, during the period from October 2019 to June 2021, who met the study protocol criteria.

Inclusion criteria

Patient with histologically confirmed endometrial carcinoma, who underwent total hysterectomy with bilateral salpingo-oophrectomy, with one of the following postoperative FIGO 2009; high-Risk endometrioid histology; stage IB grade 3 or stage II – III, or non-endometrioid histology (serous, clear cell); stage IA with myometrial invasion, IB, II or III.

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.

Pretreatment evaluation

Medical history, physical and complete pelvic examination were performed; post-operative pelvic MRI and chest CT; blood count and chemistry tests and cardiac assessment by echocardiography (for cardiac patients) were performed.

Study design

Eligible patients were randomized to one of the following arms: concurrent chemotherapy with radiotherapy [Arm A; CCRT], or external beam pelvic radiotherapy alone [Arm B; RTH]. Patients in Arm A; were treated with pelvic radiotherapy, concurrently with weekly paclitaxel. While, patients in Arm B; were treated with pelvic radiotherapy alone.

Radiotherapy technique

All patients started their treatment within 8 weeks after surgery. Patients were treated in supine position. Treatment with a full bladder and empty rectum. 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 were used. A planned volume (four-field ‘box’, 3-field or multiple field techniques with or without supplementary fields or segments) were 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.

All patients were pre-medicated with an antiemetic and anti-histaminic prior to each cycle. An adequate blood count was required in all patients before each cycle. Additional antiemetic or growth factors were given when indicated.

Patients with Stage III disease were referred to continue adjuvant chemotherapy, after finishing pelvic radiotherapy.

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.

Toxicity

All treatment related toxicities were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Acute toxicities are defined as adverse events happens from 1st day of treatment till 30 days after receiving last treatment.

Statistical Analysis

Statistical analysis of data was done by the statistical package for the social science (SPSS) using last version. 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 between variables. 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 of study protocol; 34 patients received concurrent chemo-radiotherapy [Arm A; CCRT]; and 37 patients received radiotherapy alone [Arm B; RTH].

Patient's characteristics

Table (1) summarized our patients and disease characteristics.

The median age at time of diagnosis is 66 years. The age was ranged from 52 to 77 years. Most of our patients were older than 60 years; 85.2% in CCRT arm, and 86.5% in RTH arm. Disease staging according to FIGO 2009 surgical staging system was as follow; 33 patients [46.5%] with stage Ib, 13 patients [18.3%] with stage II and 25 patients [35.2%] with stage III. Regarding histological diagnosis; 10 patients [14.1%] were Endometrioid endometrial carcinoma [EEC] grade1, 21 patients [29.6%] were EEC grade 2, 17 patients [23.9%] were EEC grade3, and 23 patients [32.4%] were with non-endometrioid histology. Lympho-vascular space invasion was present in 45 patients [63.4%].

Radiation toxicity

Table (2) illustrate incidence and grades of radiation toxicity in both arms.

Radiation therapy was tolerable for the majority of patients with mild to moderate complaints; this did not require major treatment interruption. Grade 3 toxicity were more in CCRT arm, and mainly hematological toxicity. No grade 4 toxicity were recorded in both arms. The most frequent events were diarrhea and hematological affection. No significant difference in acute toxicities between treatment groups; except for hematological affection with concurrent paclitaxel [p=0.025].

Treatment Failures and Survivals

Median follow-up period was 23 months, ranged from 13 to 32 months. During follow-up, 12 events of treatment failure were occurred. Ten patients [14.1%] had a treatment failure; 2 patients had loco-regional failure, 6 patients had distant metastases and 2 patients had both regional and distant failures. Patterns of treatment failure are summarized in Table (3).

From 71 patients; 9 deaths were happened; 4 in CCRT arm and 5 in RTH arm. Estimated 2-years survival 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]. Estimated survivals are represented in Table (4) and Figures (1) & (2).

Table (1): Patients and Disease Characteristics

	CCRT (n=34)	**RTH (n=37)**	**All (n=71)**
Age			
Median (Range)	66 [52 – 75]	66 [53 – 77]	66 [52 – 77]
<60	5 [14.7%]	5 [13.5%]	10 [14.1%]
≥60	29 [85.2%]	32 [86.5%]	61 [85.9%]
ECOG Performance Status			
0	12 [35.3%]	11 [29.7%]	23 [32.4%]
1	20 [58.8%]	23 [62.2%]	43 [60.6%]
2	2 [5.9%]	3 [8.1%]	5 [7.0%]
FIGO 2009 Staging			
Stage Ib	16 [47.1%]	17 [45.9%]	33 [46.5%]
Stage II	6 [17.6%]	7 [18.9%]	13 [18.3%]
Stage III	12 [35.3%]	13 [35.1%]	25 [35.2%]
Histology and Grade			
EEC G1	5 [14.7%]	5 [13.5%]	10 [14.1%]
EEC G2	10 [29.4%]	11 [29.7%]	21 [29.6%]
EEC G3	8 [23.5%]	9 [24.3%]	17 [23.9%]
Non-ECC	11 [32.3%]	12 [32.4%]	23 [32.4%]
● *Serous*	*7 [20.6%]*	*7 [18.9%]*	*14 [19.7%]*
● *Clear Cell*	*4 [11.8%]*	*5 [13.5%]*	*9 [12.7%]*
LVSI			
Yes	22 [64.7%]	23 [62.2%]	45 [63.4%]
No	12 [35.3%]	14 [37.8%]	26 [36.6%]

Table (2): Acute toxicities between treatment groups

Adverse Events	**Grade 2**		**Grade 3**		*p Value*
	CCRT	RTH	CCRT	RTH	
Any	**20 [58.8%]**	**16 [43.2%]**	**11 [32.3%]**	**2 [5.4%]**	**0.095**
Nausea/Vomiting	5 [14.7%]	1 [2.7%]	0	0	0.165
Diarrhea	11 [32.4%]	9 [24.3%]	4 [11.8%]	2 [5.4%]	0.592
Cystitis	3 [8.8%]	2 [5.4%]	0	0	0.922
Hematological	12 [35.3%]	3 [8.1%]	6 [17.6%]	0	***0.025***
● *Anemia*	*4 [11.8%]*	*3 [8.1%]*	*1 [2.9%]*	*0*	
● *Neutropenia*	*8 [23.5%]*	*0*	*5 [14.7%]*	*0*	

Table (3): Patterns of Treatment Failure

	CCRT (n=34)	**RTH (n=37)**	**All Groups (n=71)**	*p-Value*
Any Treatment Failure	4 [11.8%]	6 [16.2%]	10 [14.1%]	***0.51***
Loco-regional	2 [5.9%]	2 [5.4%]	4 [5.6%]	
Distant	3 [8.8%]	5 [13.5%]	8 [11.3%]	

Table (4): Estimated 2-Years Survivals

	CCRT	RTH	All Patients	p-value
2-years OS	87.0%	85.4%	86.2%	0.83
2-years DFS	83.2%	77.1%	80.1%	0.48

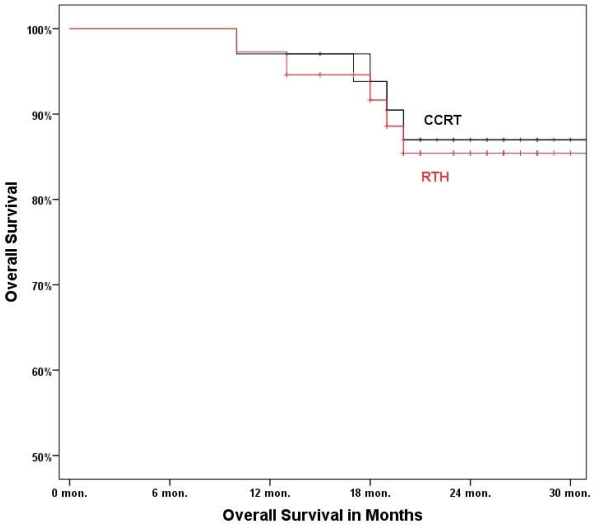

Figure (1)
Overall Survival according to Treatment Groups

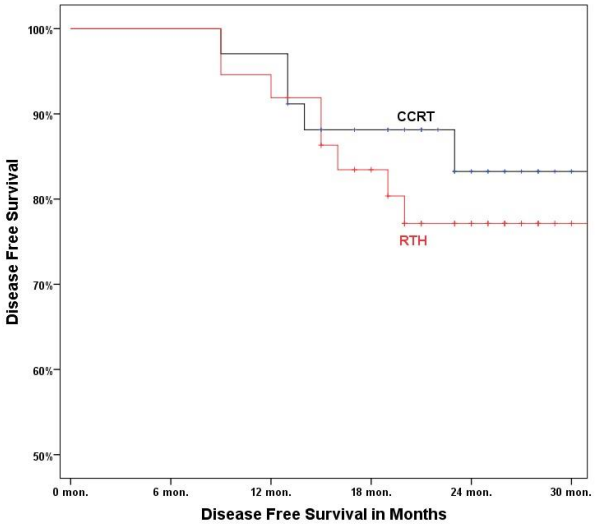

Figure (2): Disease Free Survival according to Treatment Groups

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.[6]

Pelvic external beam radiotherapy has been the standard adjuvant treatment for women with high-risk endometrial cancer for many decades. Randomized trials have compared adjuvant chemotherapy with external beam radiotherapy. Radiotherapy was shown to delay pelvic recurrence and chemotherapy was shown to delay distant metastases, but no differences in survival were found.[7] Therefore, it was logical to hypothesize that an approach that combined the methods of treatment would improve outcomes by preventing local (pelvic) and distant recurrences.

RTOG-9708 trail [8] studied combining cisplatin concurrently with pelvic radiotherapy in 46 patients. Marzi et al. [9] evaluated adding weekly paclitaxel to pelvic radiotherapy in 47 patients. Two large randomized trails tested concurrent chemoradiation either versus radiotherapy alone; PORTEC-3 trail [10] (300 patients, stage I-III), or versus chemotherapy alone; GOG-258 trail [11] (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. [12] and Binder et al. [13] 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 trail [14] and PORTEC-3 trail [10] included patients with stage I as well as higher stages. In contrast to GOG-258 trail [11] and other reports focused only on stage III patients; as done by Binder et al. [13], Cho et al. [15] and Chapman et al. [12]

Chemoradiation therapy was tolerable in our patients, as well as reported in similar studies. Grade 3 toxicities were more observed in CCRT arm; 11 from 34 patients (32%), and no grade 4 toxicity were occurred. The most common events were diarrhea and hematological affection. These rates are comparable to that reported in RTOG-9708 trail [14], as they reported grade 3 toxicities in 12 from 44 patient (27%). Marzi et al. [9] studied adding paclitaxel concurrently with adjuvant post-operative radiotherapy; they reported grade 3 toxicities in 11 from 47 patients (23%).

When comparing toxicity rates and grades between both arm, patients in CCRT arm had more hematological affection, diarrhea, nausea and vomiting. No significant difference between both arm in grade 3 toxicities, except for hematological toxicities. In PORTEC-3 [10] trail, chemoradiation was associated with more grade 2 toxicities, but grade 3-4 toxicities were significant for diarrhea and hematological events. Grade 3 diarrhea was less in our patients, as we used more advanced and conformal radiation techniques for pelvic radiotherapy, like MLC segmentation and IMRT, unlike traditional four fields box-technique used in PORTEC-3.

During follow-up, 10 (14.1%) patients showed a treatment failure; 2 patients had loco-regional failure, 6 patients had distant metastases and 2 patients had both regional and distant failure. Although, more relapses were in RTH arm (6 vs. 4 in CCRT arm); no statistical deference in our sample. Marzi et al. [9] reported 7 relapses (16%), only 2 of them were regional relapses. This quite similar to our patients in CCRT arm, 5 relapses (15%), and 2 of them were regional relapses. In RTOG-9708 trail [8], in which cisplatin was given concurrently with radiotherapy, 10 relapses (21% of 44 patients) were occurred, 4 of them were regional relapses. In contrast to GOG-258 trail [11], pelvic and distant failures were 11% and 27% respectively, as patients were with more advanced disease stage.

All of our patients were follow-upped at least for 2 years. 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 trail [8] [using cisplatin] and Marzi et al. [9] 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 trail [10], 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.

Conclusion:

Adding concurrent paclitaxel to pelvic radiotherapy in high-risk endometrial cancer patient is safe and tolerable, and tends to decrease treatment failures, even though this not translated to OS nor DFS improvement.

Conflict of Interests

The authors declare that they have no conflict of interests.

References:

[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.

[2] Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types.

Lancet Oncol. 2014;15(7):e268-78.

[3] Beck TL, Schiff MA, Goff BA, et al. Robotic, Laparoscopic, or Open Hysterectomy: Surgical Outcomes by Approach in Endometrial Cancer. J Minim Invasive Gynecol. 2018;25(6):986-993.

[4] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Obstet. 2009;105(2):103-104.

[5] Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27(1):16-41.

[6] Mundt AJ, Murphy KT, Rotmensch J, et al. Surgery and postoperative radiation therapy in FIGO Stage IIIC endometrial carcinoma. Int J Radiat Oncol. 2001;50(5):1154-1160.

[7] Alvarezsecord A, Havrilesky L, Baejump V, et al. The role of multi-modality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. Gynecol Oncol. 2007;107(2):285-291.

[8] Greven K, Winter K, Underhill K, et al. Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. Gynecol Oncol. 2006;103(1):155-159.

[9] De Marzi P, Frigerio L, Cipriani S, et al. Adjuvant treatment with concomitant radiotherapy and chemotherapy in high-risk endometrial cancer: A clinical experience. Gynecol Oncol. 2010;116(3):408-412.

[10] de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(3):295-309.

[11] Matei D, Filiaci V, Randall ME, et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 2019;380(24):2317-2326.

[12] Chapman BV, Swanick CW, Ning MS, et al. Adjuvant combined-modality therapy for stage IIIC endometrioid and non-endometrioid endometrial cancer. Gynecol Oncol. 2019;154(1):22-28.

[13] Binder PS, Kuroki LM, Zhao P, et al. Benefit of combination chemotherapy and radiation stratified by grade of stage IIIC endometrial cancer. Gynecol Oncol. 2017;147(2):309-314.

[14] Greven K, Winter K, Underhill K, et al. Preliminary analysis of RTOG 9708: adjuvant postoperative radiotherapy combined with cisplatin/paclitaxel chemotherapy after surgery for patients with high-risk endometrial cancer. Int J Radiat Oncol. 2004;59(1):168-173.

[15] Cho H, Nam B-H, Kim SM, et al. A Phase 2 Trial of Radiation Therapy With Concurrent Paclitaxel Chemotherapy After Surgery in Patients With High-Risk Endometrial Cancer: A Korean Gynecologic Oncologic Group Study. Int J Radiat Oncol. 2014;90(1):140-146.