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Sequential Adjuvant Chemotherapy and Radiotherapy in Treatment of Early Stage Endometrial Carcinoma: Single Institutional Experience

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Abstract

Background: Aim was to evaluate the additional benefit of adjuvant chemotherapy in patients of early stage endometrial carcinoma (EC) with adverse features.

Materials and methods: Between June 2006 and July 2011, 56 patients with EC after surgery were randomized to receive either adjuvant radiotherapy (RT) [35 patients] or adjuvant sequential chemotherapy and radiotherapy (CRT) [21 patients]. Median age was 57.6 years (40-80). Predominant stages were FIGO IB (44.6%) and IIA (26.7%). Mean body mass index was 35.9 kg/m^2 (23-72).

Results: Median follow-up was 55 months (6-60). The Kaplan-Meier estimates for loco regional control (LRC), distant metastasis control (DMC) and overall survival (OS) for RT and CRT arms were; 85.7% vs. 74.2% (p 0.04), 85.7% vs. 85.7% (p 0.9) and 82.8% vs. 81% (p 0.8) respectively. Patients in CRT arm had earlier and higher pelvic recurrences {hazard ratios of 2.21 (1.45-7.85)}. Acute hematological grade3 toxicity was higher in CRT arm (9.5%) and no difference in acute or delayed non-hematological toxicities was seen between two arms.

Conclusion: Adjuvant chemotherapy in patients with EC after surgery is associated with inferior LRC and no additional benefit in DMC and OS. If adjuvant chemotherapy is considered it shall be given after adjuvant radiotherapy.

Keywords: Early stage; Endometrial carcinoma; Adjuvant radiotherapy; Adjuvant chemotherapy; Treatment outcomes

Abbreviations: EC: Endometrial Carcinoma; RT: Radiotherapy; CRT: Chemotherapy Radiotherapy; FIGO: International Federation of Gynecology and Obstetrics; LRC: Loco Regional Control; DMC: Distant Metastasis Control; PFS: Progression Free Survival; OS: Overall Survival; PORTEC: Post-Operative Radiation Therapy in Endometrial Cancer; GOG: Gynecologic Oncology Group; IRB: Institutional Ethical Review; CT: Computed Tomography; CTV: Clinical Target Volume; PTV: Planning Target Volume; 3DCRT: Three Dimensional Conformal Radiation Therapy; BMI: Body Mass Index

Introduction

Endometrial carcinoma (EC) is the tenth most common and the second most common gynecologic malignancy in women in the Saudi Arabia [1]. Surgery is the primary treatment involving a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and pelvic washings, with five year survival rates of 78% [2,3]. Randomized trials by Post-operative Radiation therapy in endometrial cancer (PORTEC) and Gynecological Oncology Group 99 (GOG-99) have shown significant reduction of the risk of pelvic and vaginal recurrence by adjuvant radiotherapy, although a survival benefit is not yet proven [4,5]. Thus radiotherapy remains mainstay of adjuvant treatment.

The role of chemotherapy alone in postoperative management of EC has remained controversial. Large randomized trial of Gynecologic Oncology Group (GOG 122) has shown the improvement in both progression free survival (PFS) and overall survival (OS) at 52 months with the use of adjuvant chemotherapy alone compared with adjuvant radiotherapy in stage III and IV patients (without evidence of hematogenous metastases) after surgery [6]. Contrary, two large randomized trials have shown that adjuvant chemotherapy alone was not better than adjuvant radiotherapy alone with no difference in PFS and OS rates in patients with early stage EC [7,8].

Benefit of sequential adjuvant chemotherapy and radiotherapy was seen in advanced stage endometrial carcinoma by NSGO/EORTC and MaNGO studies with 36% reduction in the risk for relapse (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.41-0.99; p 0.04) [9]. However, both trials of sequential adjuvant treatment failed to see any significant differences in the OS.

Theoretically, adjuvant chemotherapy after surgery may delay the curative radiotherapy which may result in locoregional control. The aim of our study was to evaluate impact of sequential chemotherapy and radiotherapy in patients with early stage endometrial carcinoma with adverse features.

Materials and Methods

After approval from Institutional Ethical Review Board (IRB) committee, patients referred to our department between June 2007 and July 2011 were selected when they met the following eligibility criteria:

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(1) histological confirmed endometrial carcinoma, (2) International Federation of Gynecology Obstetrics (FIGO) stage IA-IIB, (3) presence of adverse histological features (grade 3, lymphovascular invasion), (4) Eastern Cooperative Oncology Group performance status 0-2; and (5) normal hematological parameters (hemoglobin ≥ 10 g/dL, white blood cell ≥ 4000/mm^3, absolute neutrophil count ≥ 1500/mm^3 and platelets ≥ 100 000/mm^3), normal hepatic parameters (serum bilirubin level ≤ 1.5 mg/dL and liver transaminase levels ≤ 3 times upper normal limit) and normal renal function (serum creatinine level ≤ 1.5 mg/dL).

Patients who had metastatic or recurrent disease or poor functional status were excluded.

After selection, patients were randomized to receive; Arm A: adjuvant pelvic radiotherapy and Arm B: adjuvant sequential chemotherapy followed by pelvic radiotherapy.

Treatment protocol

Radiotherapy: All patients were simulated using Siemens Emotions 6 computed tomography (CT) simulator. Contrast enhanced axial images of 5 mm slice thickness were obtained from the top of fourth lumbar (L4) vertebra to 5 cm below ischial tuberosities. After the acquisition of CT data, delineation of contouring of CTV [vaginal, cuff, parametria, external, internal iliac, presacral and common iliac lymph nodes], planning target volume (PTV) = CTV + 1 cm margin, and critical structures (urinary bladder, rectum, small bowel) was performed using Varian Eclipse Contouring software by two radiation oncologists. After contouring treatment planning for conformal therapy (3DCRT) was carried out by two medical physicists. Treatment plans were made using box field technique for 3DCRT. The PTV was prescribed to 45-50.4 Gy in 25-28 fractions, 1.8 Gy per fraction, one fraction per day. Efforts were made to receive 45-50.4 Gy to 95% of PTV and to reduce hot spots less than 120%. During planning, total doses to the small bowel, rectum and bladder were constrained to < 40Gy, < 45Gy and 45 Gy respectively. After completion of pelvic external beam irradiation, high dose rate (HDR) intravaginal brachytherapy (IVBT) was given. Total IVBT dose was 15 Gy delivered in 3 sessions (each session three days apart). The reference point for dose prescription was 0.5 cm from surface of vaginal applicators figure 1.

Chemotherapy: In arm B, adjuvant chemotherapy was given initially 6 weeks after surgery, before starting radiation therapy. Adjuvant chemotherapy consisted of four cycles of paclitaxel (175mg/m^2) and carboplatin (350 mg/m^2) every 21 days based on Lupe K, et al. Protocol [10]. Dose modifications were done according to side effects and tolerance of patients.

Toxicity and Response evaluation: During radiation therapy, patients were evaluated every week for weight, performance status, hematology/chemistry and side effects. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, were used to score acute radiation toxicity (≤ 90 days from start of radiation therapy). The Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria were used to score radiation toxicity persisting beyond 90 days from the completion of radiotherapy.

After completion of therapy, periodic follow ups were carried out every 3 months for first two years and every 6 months subsequent 3rd to 5th year with physical and per vaginal examination, pap smear and CT chest, abdomen and pelvis.

Statistical analysis: The primary endpoints were locoregional and distant control, PFS and OS. Secondary endpoints were toxicity profile. The times to last follow up evaluation, appearance of local and distant relapse and death were calculated from date of starting treatment. DFS was defined as the duration between the entry date and the date of documented disease reappearance, death from cancer and/or last follow-up (censored). OS was defined as the duration between the entry date and the date of patient death or last follow-up (censored). Probabilities of locoregional/distant control, PFS and OS were determined with the Kaplan-Meier method. The comparisons for various endpoints were performed using log rank test and Cox regression analysis. Univariate and multivariate analyses were also performed for different prognostic factors. All statistical analyses were performed using the computer program SPSS version 16.0.

Results

Median follow up was 55 months (range: 6-60 months). There was no significant difference in patients' characteristics in both treatment subgroups table 1. Majority of study cohort was with cormorbids (29 patients, 51.8%) and median BMI was 35.9 kg/m^2 (range: 28-72)**.** Most common stage was, IB in 25 patients (44.6%) followed by IIA in 15 patients (26.7%) and node positive (N1) disease in 4 patients (7.1%).

Median time between surgery and radiotherapy in arm A was 7.1 weeks (range: 5-24) and in arm B was 13 weeks (11-18) p value 0.02. The median dose to PTV was 47.5 Gy (range: 45-50.4)in both arms and IVBT dose was 15 Gy at 0.5 cm from surface of applicators in both arms and mean radiotherapy duration was 6.5 weeks (range: 6- 8).

Toxicity profile

Radiotherapy treatment was generally well tolerated by all patients in both arms with grade 1 and 2 acute side effects table 2. However, in chemotherapy/radiotherapy arm, two patients developed febrile Neutropenia (9.5%) during chemotherapy, which required hospitalization and Granulocyte- colony stimulating factor (GCSF) support. Late toxicity was seen only in one patient in radiotherapy arm, who presented with sub-acute intestinal obstruction which was managed conservatively.

Locoregional control, distant control and overall survival rates

The Kaplan-Meier estimates of locoregional control, distant

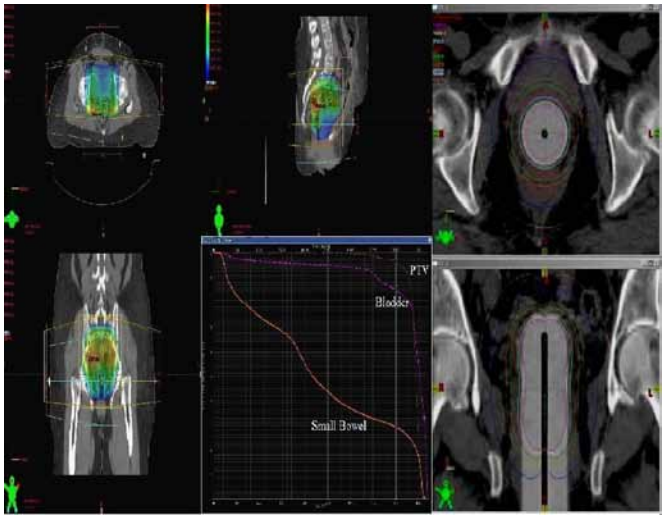

Figure 1: Pelvic box field technique using three dimensional conformal external radiation therapy plan delivering 45 Gy in 25 fractions followed by vaginal high dose rate brachytherapy by using vaginal single channel applicator.

Variables	Radiotherapy Alone N=35 (62.5%)	Sequential Chemotherapy and radiotherapy N=21 (37.5%)	P value
Comorbids (DM/HTN) Yes No	 18 (51.5%) 17 (48.5%)	 11 (52.4%) 10 (47.6%)	 0.9
FIGO Stage IA IB IIA IIB	2 (5.7%) 16 (45.7%) 9 (25.8%) 8 (22.8%)	- 9 (43.0%) 6 (28.5%) 6 (28.5%)	 0.6
Cell Type Endometroid Serous papillary Clear cell	33 (94.2%) 1 (2.9%) 1 (2.9%)	19 (90.5%) 2 (9.50%) -	 0.8
Pathological grade G1 G2 G3	 5 (14.2%) 12 (34.3%) 18 (51.5%)	 4 (19.0%) 8 (38.0%) 9 (43.0%)	 0.9
LVI Yes No	 12 (34.3%) 23 (65.7%)	 6 (28.5%) 15 (71.5%)	 0.7
ER/ PR Receptors Positive Negative unknown	 6 (17.1%) 7 (20.0 %%) 22 (62.9%)	 2 (9.5%) 4 (19.0%) 15 (71.5%)	 0.8
LN Positive Negative	 3 (8.6%) 32 (91.4%)	 1 (4.8%) 20 (95.2%)	 0.8
Squamous Metaplasia Yes No	 3 (8.6%) 32 (91.4%)	 1 (4.8%) 20 (95.2%)	 0.9
Dose RT 45 Gy EBRT + VBT 15 Gy 50.4 Gy EBRT+ VBT 15 Gy	 23 (65.7%) 12 (34.3%)	 11 (52.4%) 10 (47.6%)	 0.8

DM= diabetes, HTN= hypertension, FIGO= International Federation of Gynecology and Obstetrics, G= grade, LVI= lymphovascular invasion, LN= lymph nodes, EBRT= external beam radiation therapy, VBT= vaginal brachytherapy, RT= radiation therapy, ER= estrogen receptors, PR= progesterone receptors

Table 1: Patients characteristics according to adjuvant treatment category.

Treatment subgroups	Hematological		Skin		Small Bowel		Proctitis		Cystitis		Vagintis (discharge, pain)	
	G <3	G>3	G <3	G >3	G <3	G>3	G <3	G >3	G <3	G >3	G <3	G >3
Arm A: Adjuvant radiotherapy alone N=35	A 1 N 0 T 0	0 0 0	DD 2 (5.7%) WD 3 (8.5%)	0 0	NV 5 (14.3%) AC 3 (8.5%)	0 0	2 (5.7%)	0	1(2.8%)	0	2 (5.7%)	0
Arm B: Adjuvant chemotherapy and radiotherapy N=21	A 2 (9.5%) N 3 (14.2%) T 4 (19.0%)	0 2(9.5%) 0	DD 1 (4.7%) WD 2 (9.5%)	0 0	NV 3 (14.2%) AC 2 (9.5%)	0 0	2 (9.5%)	0	1 (4.7%)	0	2 (9.5%)	0

A= Anemia, N= Neutropenia, T= thrombocytopenia, DD=dry desquamation, WD= wet desquamation, NV= nausea and vomiting, AP= abdominal cramps

Table 2: Acute Toxicity Profile in both treatment subgroups.

Recurrence	Time of first recurrence	Salvage Treatment	Status At 55 months
Locoregional 9 patients Vaginal 2 (3.02%)	23 months 10 months	Surgery Surgery	1 dead with disease 1 disease free alive
Pelvic 7 (12.5%)	38 months 30 months 23 months	Chemotherapy	6 dead with disease 1 disease free alive
Distant 6 patients Lungs 3 (5.3%) Bones 1 (1.8%) Para-aortic nodes 2 (3.5%)	 23 months 31 months 23 months	 Chemotherapy Chemotherapy and bisphosphonates Chemotherapy	3 dead with disease 1 disease free alive 1 disease free alive 1 dead with disease

Table 3: Recurrence Pattern in patients in both treatment subgroups.

metastasis control, and overall survival were 80.1%, 85.5%, 78.6% and 81.9% respectively figure 2.

Nine patients developed locoregional recurrences (in-field). Two patients had vaginal recurrences (3.02%) and 7 patients had pelvic nodal recurrence (12.5%). Higher and earlier locoregional recurrences (5 patients, 8.9%) were seen in adjuvant chemotherapy and radiotherapy arm (p value 0.04). For all vaginal failures, salvage surgery was done and for pelvic nodal failures salvage chemotherapy was given in 5 patients (8.9%) table 3.

Distant metastases were seen 6 patients (10.7%) of whom 3 patients (5.3%) had simultaneous locoregional failures. First event was seen at 23 months of completion of treatment. All patients received salvage chemotherapy. No significant difference in distant control was seen between two arms. At 55 months of follow-up, 10 patients (17.8%) were dead. Of whom 6 patients (10.7%) died of non endometrial cancer related causes. No difference in DFS and OS was found between two treatment arms.

Further univariate and multivariate analyses were carried out table 4. Chemotherapy, BMI > 30 Kg/m^2 and LVI were found poor prognostic factors for locoregional failure (*p* 0.03, *0.02* and *0.03* respectively). For distant failure, FIGO stage was poor prognostic factor (*p 0.02*) and for OS, BMI and FIGO stage were poor prognostic factors (*p 0.01* and 0.02 respectively).

Variable	Locoregional Control P value OR (95% CI)	Distant Metastasis Control P value OR (95% CI)	Overall Survival P value OR (95%CI)
Age (< 50 vs. > 50 years)	0.33 0.93 (0.90-1.50)	0.66 1.10 (0.89-2.00)	0.71 0.50 (0.10-2.41)
Cormorbids (Yes vs. No)	0.98 0.88 (0.67-0.97)	0.901.80 (0.79-2.10)	1.00 1.80 (0.79-2.10)
FIGO stage (<IB vs. >IB)	0.75 0.50 (0.10-2.41)	**0.02 3.65 (1.81-9.65)**	**0.01 3.85 (1.91-10.35)**
N stage (N0 vs. N1)	0.77 1.10 (0.89-2.00)	0.661.10 (0.89-2.00)	0.56 1.21 (1.10-2.10)
BMI kg/m^2 (>30 vs. <30)	**0.02 3.45 (1.61-9.45)**	0.56 1.10 (0.89-2.00)	**0.02 3.65 (1.81-9.65)**
Cell type (Endometroid vs. non Endometroid)	0.48 1.21 (1.10-2.10)	0.60 1.10 (0.89-2.00)	0.77 1.21 (1.10-2.10)
Grade (<G2 vs..G3)	0.23 0.97 (0.95-1.13)	0.90 0.88 (0.67-0.97)	0.23 0.97 (0.95-1.13)
LVI (no vs. yes)	**0.05 3.34 (2.52-10.34)**	0.90 0.88 (0.67-0.97)	0.60 1.10 (0.89-2.00)
Adjuvant chemotherapy (No vs. Yes)	**0.03 2.21 (1.45-7.85)**	0.44 0.93 (0.90-1.50)	0.70 0.50 (0.10-2.41
EBRT dose (45 Gy vs. 50.4)	0.45 0.78 (0.23-2.38)	0.450.78 (0.23-2.38)	0.56 1.10 (0.89-2.00)
Squamous metaplasia (Yes vs. No)	0.85 1.80 (0.79-2.10)	0.400.78 (0.23-2.38)	0.33 0.93 (0.90-1.50)

FIGO= International Federation of Gynecology and Obstetrics, BMI= body mass index, LVI= lymphovascular invasion, EBRT= external beam radiation therapy, G= grade

Table 4: Univariate and multivariate analyses of variables on locoregional control, distant control and overall survival in both treatment sub groups.

Study [references]	Stage	Radiation techniques	Chemotherapy	Sample size (n)	Follow up period (months)	Disease Free Survival	Overall survival	Grade 3 Acute toxicity incidence	Grade 3 Late toxicity
Lupe K, et al. [10]	FIGO IIIA-IVA	Pelvic RT 45 Gy ± para-aortic RT and VBT	Adjuvant Paclitaxel+ carboplatin x 4 before RT	63	24	55%	55%	12%	18%
Alvarez Secord A, et al. [11]	Retrospective FIGO IIIA- IVA	Pelvic RT 45 Gy ± para-aortic RT and VBT	NA	83	36	62%	79%	NA	NA
Geller MA, et al. [12]	FIGO III-IVA	Pelvic RT 45 Gy ± VBT	Docetaxel+ carboplatin C4→RT → Docetaxel+ carboplatin x C2	42	28	71%	90%	54%	NA
Secord AA, et al. [13]	FIGO III-IVA	Pelvic RT 45 Gy ± VBT	Three arms: 1. C→RT→C RT→C 2. C→RT	1. 5 2. 8 3. 6	36	1. 9% 2. 7% 3. 2%	1. 8% 2. 4% 3. 7%	NA	NA
Fields AL, et al. [14]	Papillary serous carcinoma	Pelvic RT 45 Gy ± para-aortic RT	Adjuvant Paclitaxel+ carboplatin x C4 before RT	30	36	54-69%	52-75%	43%	NA
Present study	FIGO IA-IIB	Pelvic RT 45 Gy +VBT 15 Gy	Two arms 1. RT alone 2. Adjuvant Paclitaxel+ Carboplatin x C4 before RT	56	55	78.6%	81.9%	9.5%	1.7%

FIGO= International Federation of Gynecology and Obstetrics, RT= radiation therapy, VBT= vaginal brachytherapy, NA= not available, xC= cycles, C= chemotherapy

Table 5: Comparison of various studies using sequential chemotherapy and radiotherapy and its impact on treatment outcomes.

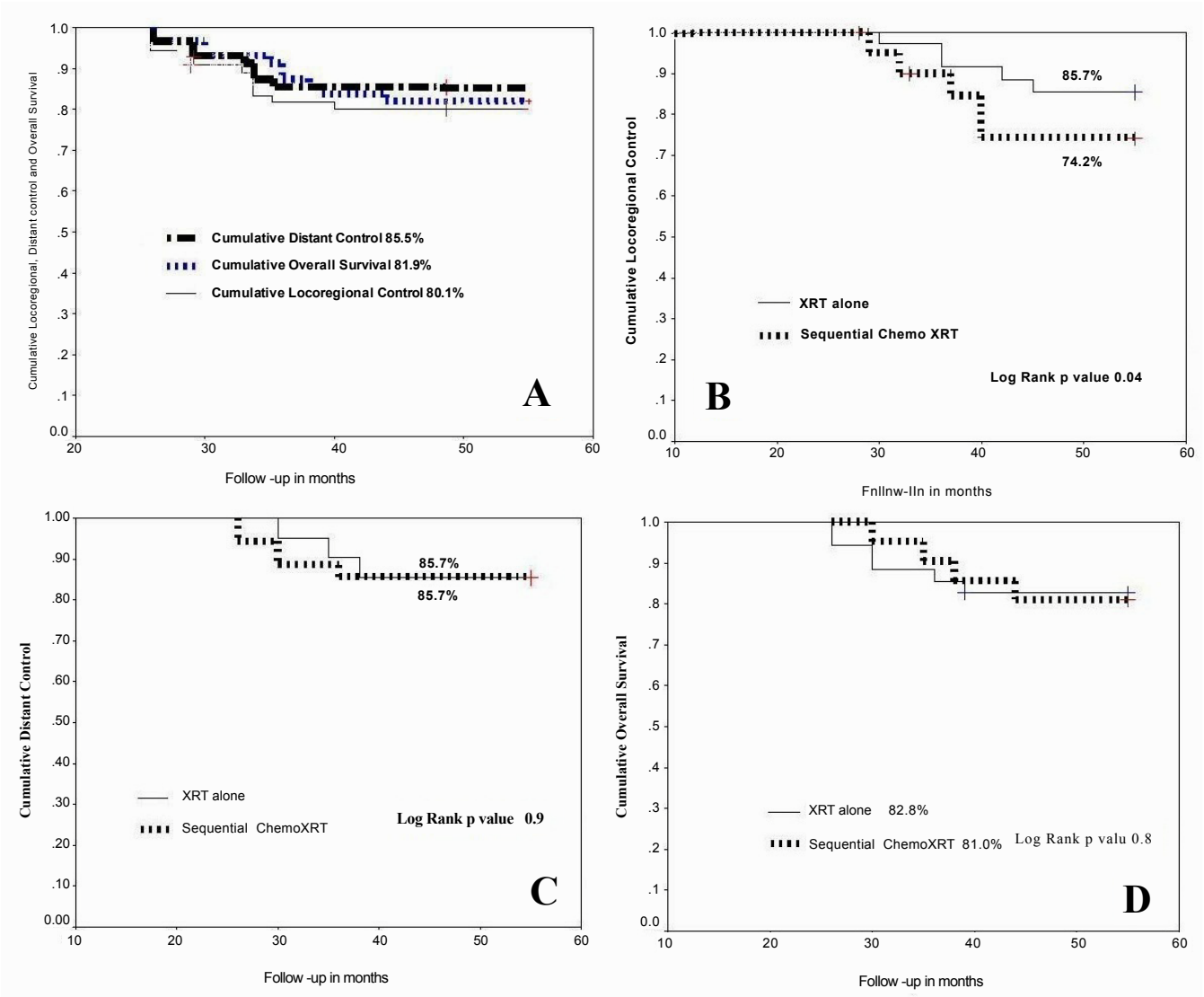

Figure 2: (a) cumulative locoregional control , distant control and overall survival rates, (b) locoregional control, (c) and (d) according to adjuvant radiotherapy and sequential chemotherapy/radiotherapy treatment subgroups.

Discussion

Adjuvant sequential chemotherapy and radiotherapy has been employed in FIGO stages III and IVA endometrial carcinoma after surgery, with minimal improvement in DFS and high hematological toxicity table 5. Our study is the first, which incorporated adjuvant sequential chemotherapy and radiotherapy in early stage (FIGO, I-IIB) endometrial carcinoma with adverse features.

The results of our study showed that adjuvant sequential chemotherapy and radiotherapy is associated with reduced locoregional control (p value 0.003) in patients with early stage endometrial carcinoma, yet there was no impact of additional adjuvant chemotherapy on distant control, DFS and OS. However sequential regimen was generally well tolerated, with grade 3 hematological toxicity encountered only in 9.5% of patients.

The possible explanation for high locoregional recurrences in adjuvant sequential chemotherapy and radiotherapy patients can be explained by delayed pelvic radiotherapy, i.e. mean time between surgery and radiotherapy was 13 weeks (11-18). However, previously published studies of adjuvant sequential regimen in advanced stage endometrial carcinoma remained fail to document poor locoregional control because of shorter follow up period (36 months) [10,11,12,13].

No improvement in distant control and DFS and decreased toxicity in patients who received adjuvant sequential chemotherapy and radiotherapy can be explained by high body mass index (mean, 35.9 kg/m^2 (range: 28-72) in our study cohort, which perhaps caused dose capping and subsequently led to suboptimal chemotherapy dose [15]. Presence of co-morbidities (51.8%) and high body mass index in our cohort was associated with decreased OS, as also reported by other studies [16].

Potential strength to support our data was reasonable follow up period. Our study can be criticized for its low sample size and presence of confounders (obese patients with co-morbidities).

Conclusion

Our results did not support the incorporation of sequential chemotherapy in adjuvant care of early endometrial carcinoma. However future large trials should consider the appropriate sequencing of chemotherapy, i.e. Adjuvant chemotherapy followed by radiotherapy or adjuvant radiotherapy followed by chemotherapy or sandwich radiotherapy between chemotherapy in early stage endometrial carcinoma with adverse features.

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