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The Addition of Sequential Locoregional Radiation Therapy after Adjuvant Chemotherapy for Endometrial Cancer Patients with Para-Aortic Involvement - The Impact on Recurrence and Survival

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Abstract

Purpose: The benefit of adjuvant Radiation Therapy (RT) after surgical resection and chemotherapy is not well defined for patients with endometrial cancer patients with Para-Aortic (PA) nodal involvement (FIGO stage IIIC2). The purpose of this study was to compare survival and patterns of failure after treatment with or without adjuvant RT.

Methods and Materials: Consecutive patients with FIGO stage IIIC2 endometrial cancer treated from 2000-2010 were identified across three cancer centers, 1 of which does not routinely offer adjuvant RT in this setting. Characteristics and outcomes of patients treated with or without RT (RT vs. NRT) were compared with descriptive and multivariable analyses.

Results: 65 patients were identified. Median follow-up was 114 months. 55 (85%) received chemotherapy and 33 (51%) received adjuvant RT. Rates of freedom from locoregional relapse at 5 years was 58.8% in the RT group and 42.3% in the NRT group (p = 0.18). Median DFS trended in favour of the RT group (not reached vs. 26.9 months, p = 0.18), while median OS significantly favoured the RT group (91.2 vs. 29.7 months, p = 0.04). Trends remained similar after excluding non-endometrioid histologies and after excluding patients without pathological PA nodes. However, after adjusting for age, histology, and myometrial invasion, OS and DFS for RT were numerically but not statistically better than NRT (HR for DFS 0.59, 95% CI 0.23-1.51, p=0.27; HR for OS 0.58, 95% CI 0.24-1.40, p=0.23). RT-associated toxicities consisted of grade 1 and 2 gastrointestinal and genitourinary symptoms and fatigue; grade 3 toxicities were uncommon (5%).

Conclusions: Adjuvant RT after chemotherapy in FIGO stage IIIC2 endometrial cancer was associated with numerically better but not statistically significant OS, DFS and freedom from locoregional relapse after adjusting for risk factors.

Keywords: FIGO stage IIIC2 endometrial cancer; Adjuvant radiation; Adjuvant chemotherapy; Staging

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Introduction

Endometrial carcinoma is a heterogeneous entity with multiple histologies [1]. It comprises 6.5% of new cancers and is the fourth commonest cancer in women [2]. Advanced presentations are uncommon [3]. Endometrial cancer is staged according to FIGO guideline [4]. Surgical resection of all gross disease is the mainstay of treatment. Optimal adjuvant treatment is less certain, particularly in patients with FIGO stage III disease, which includes patients with a wide variety of pathologic risk factors.

Table 1: Patient, disease and treatment characteristics.

		RT (n=33)	No adjuvant RT (n=32)
Age at diagnosis (years)		60 (range 31-77)	65 (range 35-86)
FIGO grade (2 missing)	1	4	3
	2	6	4
	3	23	23
Histology	Endometrioid	18	10
	Papillary serous	4	9
	Clear cell	0	3
	Undifferentiated/ carcinosarcoma	2	2
	Mixed endometrioid/ non-endometrioid	9	8
Myometrial invasion >50%		20	21
Lymphovascular invasion		27	24
Locally involved organs	Cervix	18	14
	Parametrium	2	5
	Ovary	6	12
	Fallopian tube	5	8
Tumour size (cm), median		4	4
Number of patients with pelvic lymph node sampling		21	22
Number of patients with para-aortic lymph node resection		17	24
Staging modality (missing= 1)	Pathology	17	23
	Imaging	16	8
Number of patients with pelvic washing		17	17
Number of patients with omentectomy		8	15
Adjuvant chemotherapy use		29 (88%)	26 (81%)
Number of cycles, median		3.5	6
Grade 3-4 chemotherapy adverse events		4	3

Adjuvant chemotherapy is considered standard therapy for high-risk disease because prospective studies have demonstrated a survival advantage benefit with adjuvant chemotherapy in high-risk endometrial cancer [5-8]. External Beam Radiation Therapy (EBRT) is also often considered in patients with positive nodes; involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum; or pathologic risk factors for pelvic recurrence [9]. However, it is less clear whether adjuvant RT improves locoregional control or survival compared to chemotherapy alone. Many studies looking at the effectiveness of RT include a heterogeneous mix of all stage III and IV patients, making it difficult to tease out the benefit for specific risk factors.

FIGO stage IIIC is divided into IIIC1 (pelvic nodal involvement) and IIIC2 (para-aortic or PA nodal involvement) [10]. PA nodal involvement predicts poorer survival [11] in some studies but not others [7,8,12-16]. Internationally, guidelines and clinical practices for stage III endometrial cancer vary [17-20]. Further complicating decision-making is the risk of RT-associated side effects. One study associated EBRT with a 37% increase in Grade 1-3 diarrhea, 34% more lethargy, and increased occurrence of genitourinary and skin toxicities [21]. This is a report of the use, efficacy and side-effects of adjuvant RT in addition to chemotherapy compared with chemotherapy alone for FIGO stage IIIC2 endometrial cancer as used across a broad geographic region with universal access to health care.

Methods and Materials

After approval through the relevant institutional health research ethics boards, we identified consecutive patients with a new diagnosis of endometrial cancer from January 1, 2000 to December 31, 2013 through regional cancer registries. Patients evaluated through three cancer centers providing 100% of the RT in two geographically-defined jurisdictions were included. After initial case identification, co-investigators manually verified PA nodal involvement by retrospective chart review. A patient was deemed to have stage IIIC2 disease if PA lymph nodes were involved pathologically or were abnormal by size criteria on pre-operative Computed Tomography (CT) imaging [22,23]. Demographic, pathology, treatment (use and type of chemotherapy, RT use, dose, fractionation, volume and brachytherapy use, type and extent of surgery and cancer outcome endpoints including survival and date and type of relapse were abstracted retrospectively using a standardized data dictionary.

Descriptive statistics summarized demographic, disease characteristics, treatment and patterns of relapse. Overall Survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Patients were censored at last follow-up. Disease-Free Survival (DFS) was the interval from the date of diagnosis to the date of first relapse, progression, death, or last follow-up. Freedom from locoregional relapse was defined from the data of diagnosis to the date of locoregional relapse, including in-field (if RT was used) or out-of-field abdominal, pelvic or vaginal recurrence but

Table 2: Adjuvant radiation treatment.

RT type	External beam RT only: 20 Both external beam RT and brachytherapy: 13
RT technique	3D-CRT: 31 Missing: 2
External beam RT targets	Pelvic only: 5 Paraaortic and pelvic: 27 Missing: 1
External beam RT total dose (cGy), median	4500 (range: 4000-6500)
External beam RT total # fractions, median	25 (range: 22-35)
Brachytherapy source	Iridium-192: 8 Caesium-137: 2 Unknown: 3
Brachytherapy total dose (cGy), median	500 (range: 300-1600)
Brachytherapy fractionation	1 fraction: 8 2 fractions: 1 3 fractions: 3

RT: radiation therapy; 3D-CRT: 3-dimensional- conformal radiation therapy; cGY: centigray.

excluding visceral organ metastases. Kaplan-Meier survival analyses were used to assess OS, DFS, and freedom from locoregional relapse globally and comparing RT with no RT (NRT) cohorts. The log-rank statistic was used to test the significance of survival differences between treatment cohorts. Multivariable Cox proportional hazard regression models were constructed to evaluate variables significantly influencing survival outcomes. Statistical significance was set at $p< 0.05$. Statistical analyses were performed on R version 3.0 (NZ) or SPSS v24 (Armonk, NY).

Results

A total of 65 Stage IIIC2 patients were identified from the two geographic regions. Table 1 describes patient, disease and treatment characteristics for the patients who received RT (n = 33) or no RT (n = 32). 55 (85%) patients received adjuvant chemotherapy. All patients received a combination of platinum and taxane agents. Patients in the NRT group were older, received more chemotherapy cycles, included more patients with serous or clear cell histology, were more likely to be from the institution with a policy that does not offer adjuvant RT in the setting of involved PA nodeds, and more likely to have resection of PA nodes. FIGO grades, Lymphovascular Invasion (LVI), and the presence of myometrial invasion were similar between the two groups. Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) [24] grade 3-4 events from chemotherapy were infrequent but similar between groups (RT 9% vs. NRT 12%).

Table 2 describes technical details of adjuvant RT. All patients had EBRT using 3D-CRT. 13 patients (39%) received both EBRT and a vaginal brachytherapy boost. 27 patients (81%) had RT to both pelvic and para-aortic nodes and 5 patients (15%) had RT to the pelvis alone. Of five patients with stage IIIC2 who received only pelvic RT, two had chart notes about limiting RT volume due to co-morbidities and three cases were staged as IIIC2 on the basis of enlarged PA nodes on CT imaging.

Figure 1 and 2 illustrate the Disease-Free Survival (DFS) and Overall Survival (OS) by treatment cohort. The actuarial median OS was 91 months for the RT cohort and 30 months for the NRT group (p=0.04). The median DFS was not reached for the RT group and was 27 months for the NRT group (p=0.18). Actuarial 5-year OS was 54% (95% CI 38% - 75%) in the RT group and 28% (95% CI 16%-50%) in the NRT group. Actuarial 5-year DFS was 54% (95% CI 39% - 75%) in the RT group and 39% (95% CI 24%-63%) in the NRT group. Table 3 describes sites of recurrence and reasons for death. Actuarial rates of freedom from locoregional relapse at 5 years were 59% in the RT group and 42% in the NRT group (p = 0.18) (Supplementary Figure 1).

Table 3: Patterns of relapse and death.

		RTused (n=33)	No adjuvant RT (n=32)
Disease relapse	Overall (%)	14 (42%)	19 (59%)
	Vaginal	4	2
	Pelvic	2	3
	Abdominal	8	14
	Simultaneous distant relapse	5	5
Death (%)		14 (42%)	25 (78%)
Endometrial cancer related death (%)		9 (27%)	20 (63%)

*Abdominal relapse was defined as all disease relapse in the abdominal cavity beyond the confines of pelvis, including recurrence in peritoneum. Visceral metastasis including liver metastasis was included in distant relapse.

Table 4: Multivariate analysis of DFS and OS (n=47, excluding cases with missing values).

Factor	DFS		OS	
	HR	p-value	HR	p-value
RT Yes vs. No	0.67 (0.32-1.42)	0.298	0.57 (0.28-1.16)	0.122
Age	0.997 (0.96-1.03)	0.858	1.01 (0.98-1.04)	0.617
Histology Other vs. Endo	1.45 (0.66-3.21)	0.358	1.28 (0.62-2.64)	0.511
Myometrial Invasion Yes vs. No	1.38 (0.67-2.86)	0.387	1.65 (0.83-3.29)	0.156

DFS: Disease-Free Survival; OS: Overall Survival; HR: Hazard Ratio; RT: Radiation Therapy; Endo: endometrioid histology.

Table 5: Toxicities from RT.

GI adverse events	Diarrhea	Grade 1	**14**
		Grade 2	4
		Grade 3	1
	Nausea	Grade 1	6
		Grade 2	0
		Grade 3	2
	Pain	Grade 1	7
GU adverse events		Grade 1	5
Fatigue adverse events		Grade 1	10
		Grade 2	2

In multivariable analysis (Table 4), age, histology, and myometrial invasion was not significantly associated with OS or DFS. After controlling for these factors, RT use was not statistically associated with OS or DFS, and the hazard ratios (HR) associated with RT use were numerically similar for OS and DFS and favoured RT (HR for DFS 0.67, 95% CI 0.32-1.42, p=0.27; HR for OS 0.57, 95% CI 0.28-1.16, p=0.12). After excluding serous and clear cell carcinoma, trends in OS and DFS remained similar (Supplementary Figure 2). In the 41 patients who had surgical evaluation of para-aortic lymph nodes, OS and DFS were numerically better without statistical significance in the RT group (Supplementary Figures 3). DFS and OS were also analyzed after excluding patients who received treatment contrary to institutional recommendation e.g. RT in one centre that routinely recommended no RT; no RT in two centres that recommended RT (Supplementary Figure 4). OS and DFS were still numerically better

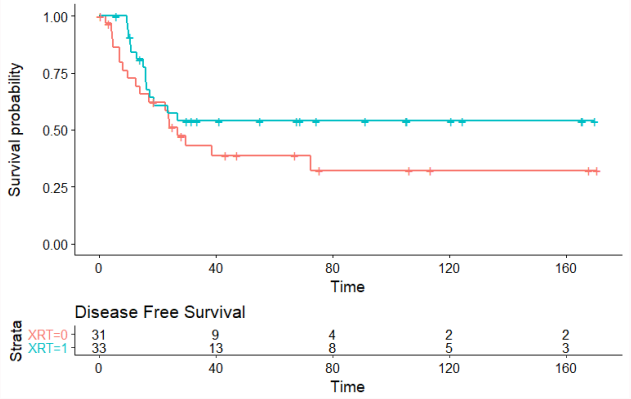

Figure 1: Disease-free survival (DFS) for patients who received adjuvant RT (RT) vs. no adjuvant RT (NRT).

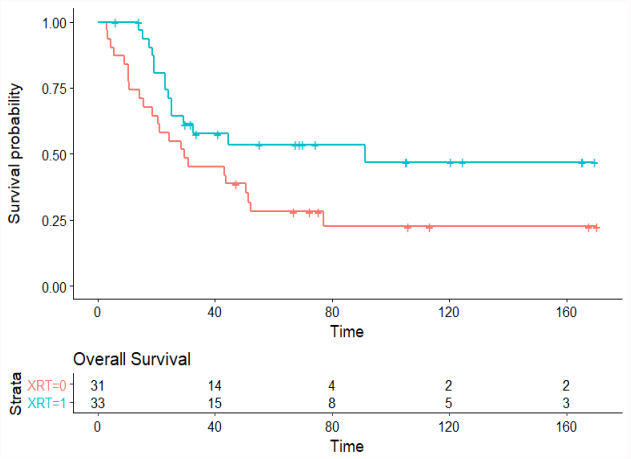

Figure 2: Overall survival (OS) for patients who received adjuvant RT (RT) vs. no adjuvant RT (NRT).

without statistical significance in the RT group. Common acute side effects of RT included grade 1 or 2 diarrhoea, nausea, abdominal pain and fatigue. Grade 3 or 4 adverse events were rare (Table 5).

Discussion

This study represents real-world data set to compare outcomes between patients who received and did not receive adjuvant RT in a multicentre, population-based cohort of patients with stage IIIC2 endometrial cancer. One of the participating centres commonly recommended no adjuvant RT for stage IIIC2 patients considering para-aortic nodal involvement to be a predictor of systemic relapse and the added toxicity of adjuvant RT outweighing the potential benefit of locoregional control. Strength of the current study was inclusion of patients from centres with varying institutional policies which would have reduced the impact of individual physician selection biases.

Our study shows that while associated with numerically improved relapse rates and DFS, the addition of RT in stage IIIC2 patients is not associated with statistically significant improvements in OS or DFS. The significantly longer OS associated with RT group is attributed to the effect of confounders after multivariable analysis. Recently presented GOG-0258 trial included FIGO stage III or IVA endometrial cancer and stage I or II clear cell or serous endometrial cancer with positive cytology, and compared chemo RT with four cycles of cisplatin with 6 cycles of chemotherapy alone [25]. While vaginal, pelvic and para-aortic recurrences decreased with the addition of RT, Recurrence-Free Survival (RFS) and OS were similar between the two groups. Given the heterogeneity of the population, underpowered subgroup analysis, and use of chemo RT and 4 cycles of chemotherapy as opposed to 6 full cycles of chemotherapy and sequential RT, GOG 0258 is underpowered to provide level I evidence for the role of sequential adjuvant RT specifically in stage III or IIIC2 patients after 6 cycles of chemotherapy. Our study confirms that after controlling for risk factors, RT may not be associated with survival benefit but contributes to a decrease in relapse.

After adjusting for potential prognostic variables, the trend towards better DFS and OS with RT remained but was not statistical significant in the current study. Multivariable analyses were hampered by heterogeneity of staging methods and small sample sizes. Some of the previous retrospective studies have shown that RT use was associated with improved OS and DFS, while others do not [26-37]. Most of the studies include all stage III or IIIC patients and may not be directly applicable to stage IIIC2 patients. To our knowledge, there is only one other real-world study published on outcomes of a homogeneous stage IIIC2 endometrial cancer. This study reports on a single institutional experience on the outcomes and patterns of failure in 72 patients with stage IIIC2 endometrial carcinoma. Sixty six percent of patients received chemotherapy and Radiation Therapy (RT), while 28% received chemotherapy alone (CT) (i.e., no RT). Distant metastasis was the most common pattern of failure (73%). Their data showed comparable outcomes results to our study, but did not show an association between survival and receipt of RT in multivariable analysis [28].

In the current study, the RT group had numerically lower pelvic and abdominal recurrence rates compared to the NRT group. While distant relapse rates were similar between the RT and NRT groups (14% vs. 15%), intra-abdominal recurrences, defined as all recurrences in the abdominal cavity outside of the pelvis and excluding visceral metastasis, were notably higher in the NRT group than among the RT group. This may simply be related to the inherent patient selection of the NRT group or confounders not yet identified. Selection was minimized as much as possible by comparing between centers that routinely recommend adjuvant RT and a centre that does not routinely recommend RT for stage IIIC2 patients. A small number of events and cohort size likely also contributed to the absence of statistically significant differences.

Imaging-assisted lymph node staging in patients with endometrial cancer, via CT, sentinel lymph node biopsy, Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET), has been evaluated including in a systematic review [38-43]. PET/CT or PET/MRI has a high sensitivity and specificity to detect nodal involvement before or after surgery, and are useful in planning adjuvant RT [39,42]. In practice, PA lymph node resection may range from an extended dissection to sampling of suspicious nodes only, which confounds interpretation of outcomes. In the current study, the number of patients with three or more PA lymph nodes resected was similar between the RT and the NRT cohorts, but the intent of resection (primarily diagnostic versus primarily therapeutic) was not pre-specified in most patients. Given that the presence of pathologic PA lymph nodes could have affected the enthusiasm for or extent of RT, a review of institutional policies for surgical lymph node assessment may be beneficial.

Strengths of the current study include the multi-centre, population-based accrual from jurisdictions with a long history of institutional but different treatment guidelines. This enabled a direct comparison of retrospective results with less selection bias. Limitations include persistent inherent imbalances between the RT and NRT groups, lack of complete para-aortic staging in many patients, and the small number of patients available for study. Confounders such as imbalances in patient comorbidities and functional status may have contributed to selection bias but were not consistently reported in the available medical records. As no prospective data are available for the rare entity that is stage IIIC2 endometrial cancer, our results may be the most direct evidence currently available and provide support for the use of adjuvant RT for patients with para-aortic node-positive endometrial cancer.

Conclusions

While endometrial cancer is common, locally advanced presentations involving para-aortic lymph nodes are rare and signal a risk of disease relapse and death. The current study from a multi-centre, population-based cohort showed that adjuvant RT use was associated with potentially improved disease control, acceptable tolerability, and numerically better but statistically non-significant survival improvements among patients with surgically resected FIGO stage IIIC2 endometrial cancer who received combination chemotherapy. Although limited by a small sample size, after accounting for confounding factors, the current study provides support for an individualized patient counseling regarding the uncertain survival benefit and potential risks of adjuvant RT in patients with stage IIIC2 endometrial cancer.

Conflict of Interest

Author JJK received honorarium from Janssen, Astra-Zeneca and Astellas and participated in advisory board for BMS and Merck. All other authors have no relevant disclosure.

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