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Does prophylactic para-aortic lymphatic irradiation improve outcomes in women with stage IIIC1 endometrial carcinoma? A multi-institutional pooled analysis

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Does prophylactic para-aortic lymphatic irradiation improve outcomes in women with stage IIIC1 endometrial carcinoma? A multi-institutional pooled analysis.

Short title: **Paraaortic radiation in stage IIIC1 EC**

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States (U.S.) annually affecting >50,000 patients in the U.S. and >380,000 patients worldwide with increasing incidence and prevalence. Although most women are diagnosed with early-stage disease following surgical staging, approximately 10-15% have nodal involvement at diagnosis [1, 2]. The primary lymphatic drainage of the uterus is to the pelvic lymph nodes, although the fundus can directly drain to the para-aortic lymph nodes (PALN) [3].

Women with advanced stage EC with pelvic and PALN involvement are commonly managed with a combination of adjuvant chemotherapy and/or external beam radiation therapy (EBRT) to areas of initial disease involvement with or without vaginal brachytherapy (BT) after surgical staging [4]. In a phase 3 randomized trial Postoperative Radition Therapy for Endometrial Carcinoma (PORTEC-3), patients with high-risk EC including stage IA grade 3 with lymphovascular space invasion, stage IB grade 3, stage IIIA, IIIB, IIIC, and stage IA-III with serous and clear cell histology were randomized to either adjuvant chemoradiation versus radiation therapy (RT) only. The updated analysis of the PORTEC-3 showed significantly improved overall survival and failure-free survival with chemoradiation with largest failure-free survival benefit observed in women with stage III disease [5, 6]. Furthermore, the large randomized phase III trial Gynecologic Oncology Group (GOG-258) reported that chemoradiotherapy was associated with a lower 5-year vaginal (2% vs. 7%), pelvic and para-aortic (11% vs. 20%) lymph node recurrence than chemotherapy alone [7].

PALN involvement occurs in only about 7-8% of EC overall; however, when pelvic lymph nodes are positive for carcinoma, the risk of PALN involvement rises to 50-60% [8]. While the importance of PALN metastases as a predictor of poor patient outcome has been recognized and appropriately reflected in the International Federation of Obstetrics and Gynecology (FIGO) staging with 2 different categories of stage IIIC based on the absence (IIIC1) or the presence (IIIC2) of the PALN involvement [8, 9], the role and extent of PALN dissection in the surgical staging of EC has not been thoroughly defined [10, 11]. Although current guidelines recommend PALN dissection for selective high-risk patients [12], PALN sampling is commonly performed to avoid the morbidity of the full lymphadenectomy in the absence of prospective randomized trials showing clear therapeutic value of para-aortic lymphadenectomy [13]. In the Determining the Sensitivity of Sentinel Lymph Nodes Identified with Robotic Fluorescence Imaging (FIRES) multicenter prospective cohort study, sentinel lymph node biopsy has been shown as a safe replacement of lymphadenectomy with a 97% sensitivity to detect node-positive disease, although infrarenal PALN was identified in only 1% compared to inframesenteric PALN in 14% of all sentinel nodes [14].

Adjuvant therapy with combined modalities is commonly delivered in patients with stage IIIC EC given the high local and distant recurrence rates in this group. The treatment volume for adjuvant RT in women with FIGO stage IIIC1 is usually the vaginal cuff and pelvic lymphatics [15, 16]. Because recurrence in the paraortic regions can be common ranging from 7 – 20% in women with FIGO stage IIIC1 despite adjuvant multimodality treatment [13, 17], some physicians are reflexively recommending prophylactic radiation treatment to the paraaortic

area in women with FIGO stage IIIC1. However, there is a lack of consensus on the indications of prophylactic PALN radiation, extent of the radiation target volume and the appropriate RT dose.

Two small retrospective studies reported no significant improvement in survival endpoints with prophylactic paraoortic lymphatic irradiation in women with FIGO stage IIIC1 EC [18, 19]. While useful, these two studies were hampered with some study limitations such as the inclusion of patients who received preoperative radiation treatment[19] and the lack of adjuvant chemotherapy in many patients [18, 19].

Using a multi-institutional pooled database, the primary goal of this study is to evaluate the role of prophylactic PALN RT on survival outcomes and recurrence patterns in patients with FIGO stage IIIC1 EC treated with adjuvant chemotherapy and radiation treatment using robust statistical analyses including propensity score matching.

Materials and Methods

Following approval of the Institutional Review Board, a multi-institutional pooled data collection was conducted including 13 academic centers for women with FIGO stage IIIC1 EC who underwent surgical staging between 1995 and 2019. All patients received multimodality adjuvant therapies including chemotherapy and radiation therapy. Clinical, surgical and pathologic data were retrospectively recorded. Ineligibility criteria were defined as absence of nodal sampling, carcinosarcoma histology, receipt of neoadjuvant chemotherapy or RT, and

receipt of a single adjuvant modality (chemotherapy or radiotherapy). Patients with residual nodal and/or vaginal disease were included.

All patients underwent total hysterectomy, salpingo-oophorectomy, and lymph node assessment followed by adjuvant chemotherapy and radiotherapy. All patients had pathologically confirmed pelvic nodal involvement (FIGO stage IIIC1) without any pathologic or radiologic evidence of PALN involvement. In addition, patients treated with adjuvant BT only or unknown external radiation fields were excluded. Chemoradiotherapy treatment approaches included upfront chemotherapy followed by radiation (upfront chemo), concurrent chemoradiation (EBRT) followed by chemotherapy (concurrent), systemic chemotherapy before and after EBRT (sandwich) and upfront EBRT followed by chemotherapy (upfront RT). The sequencing approach for chemoradiotherapy was at the discretion of the physician and in line with each institution's practice. The indication for combination of EBRT and BT was left at the discretion of the treating radiation oncologist and was mainly used for patient with cervical stromal invasion. Prophylactic para-aortic field was defined as per GOG-258 where the upper border was at T11-T12 [7].

Statistical analysis:

A total of 378 patients were included in this study who fulfilled our inclusion and exclusion criteria. For the study purpose, the cohort was then divided into two subgroups, a group who received adjuvant radiation treatment to the vaginal cuff and pelvic lymphatics (286 patients) and a group who received the same RT treatment volume but with the addition of a prophylactic paraaortic radiation field (92 patients).

Descriptive statistics were used to characterize the patient cohort in terms of demographics, tumor and treatment characteristics. Chi-squared tests were performed to assess associations. Overall survival (OS) was defined from the date of surgery to the date of death from any cause. Recurrence-free survival (RFS) was defined from the date of surgery date to the date of first recurrence or progression or last follow-up. Time to endpoints were calculated by Kaplan-Meier method. Univariable and multivariable analysis were performed by Cox proportional hazard models for RFS/OS. The variables that were significant ($p<0.2$) on univariate analysis (UVA) were included in the multivariate analysis. In the presence of co-linear variables, only one variable was included in the multivariate analysis. Covariates evaluated by UVA were age, race, histology, tumor grade, FIGO 2018 stage, depth of myometrial invasion, presence of 2 or more positive nodes, presence of adnexal and cervical involvement, lymphovascular invasion (LVSI), type and sequencing of adjuvant chemoradiotherapy and radiation field extent (pelvic vs. pelvic + prophylactic PALN RT). Recurrences were categorized into 4 categories: vaginal recurrence only, pelvic +/- vaginal recurrences, PALN +/- pelvic recurrences and distant recurrences +/- pelvic and PALN recurrences.

In addition, propensity score matching were used to estimate the effect of the radiation field with the addition of prophylactic PALN RT on survival outcomes. It was conducted using 1:1 nearest neighbor propensity score matching without replacement. The propensity score was estimated using logistic regression of the radiation field on the covariates that may have impact on survival outcomes, or on the selection of radiation fields, or on both. After matching, all the covariates had a standardized mean difference below 0.1 except one (myometrial invasion, 0.13), as shown in Figure 1, indicating adequate balance. We fit Cox regression models to estimate the effect of the radiation field on survival outcomes with the matched data. Its standard error was estimated using a cluster-robust variance with matching stratum membership as the clustering variable. The p-value resulted from using the robust standard error. Statistical analyses were conducted using SPSS version 27 and R version 4.0.2 (https://www.r-project.org/).

Results

Patient characteristics

A total of 378 patients with stage IIIC1 EC met the eligibility criteria and were included in the analysis. The baseline clinical and pathologic characteristics for the entire cohort and the risk factors distribution among the 2 treatments groups (pelvic RT vs. pelvic + prophylactic PALN RT fields) are presented in Table 1. The median age at diagnosis was 62 (interquartile range (IQR), 55 - 69 years). A majority of patients had endometrioid adenocarcinoma (72%), deep myometrial invasion (greater than 50%) (71%), and presence of LVSI (79%). There were almost

as many patients with Grade 3 tumor (48%) as Grade 1 and 2 combined (52%). Adnexal and cervical involvement were present in 62 (17%) and 135 (36%) of patients, respectively. Pelvic and PALN assessment was performed in 171 patients (45%) while 207 patients (55%) had pelvic lymph node dissection only. The median number of resected lymph nodes in the entire cohort was 14 (IQR 9-21). The median number of resected lymph nodes in the pelvic RT group and pelvic + PALN group was 15 (IQR 10-22) and 12 (IQR 8-17), respectively. The median number of positive pelvic lymph nodes was 2 (IQR 1-2). A total of 17 patients had gross residual disease, 15 patients (4%) had nodal disease defined as R1 resection while 2 patients had vaginal and nodal disease (0.5%). Chemoradiation sequencing for these patients was the following: 5 patients received sequential chemoRT, 5 patients concurrent chemoRT and 7 patients received sandwich chemoRT. Pelvic RT only was delivered to 9 patients while 8 patients received prophylactic PALN RT. Most patients were treated with EBRT and brachy (71%). The median dose of EBRT delivered was 46 Gy (IQR 45-53.5 Gy). Standard radiation doses (45-50.4 Gy) were delivered to 11 patients, 5 patients received EBRT nodal boost up to 55 Gy and 1 patient with both vaginal and nodal residual disease received EBRT nodal boost and brachytherapy.

When comparing risk factors distribution among patients treated with pelvic RT and those treated with prophylactic PALN RT field, no differences were seen for age, race, LVSI, depth of myometrial invasion, cervical and adnexal involvement, and number of positive nodes (Table 1). However, patients treated with prophylactic PALN RT field were more likely to have endometrioid histology (p=0.02) and lower grade (p=0.01). As for the type of radiotherapy and chemoradiotherapy sequencing, patients treated with prophylactic PALN RT field were more

likely to receive EBRT + BT and sequential chemoradiotherapy compared to those treated with pelvic RT ($p<0.001$).

Treatment characteristics

Adjuvant chemotherapy agents included carboplatin, paclitaxel, taxotere, adriamycin and cyclophosphamide, with carboplatin-paclitaxel being the most common regimen. Of the 378 patients, 178 (47%) received upfront chemotherapy, 75 (20%) received concurrent, 106 (28%) received "sandwich", and 19 (5%) received upfront RT.

The most commonly used chemotherapy regimen was carboplatin (Area Under the Curve=6) and paclitaxel (175 mg/m^2) every 3 weeks (90%). The median number of chemotherapy cycles was 6 (IQR 4-6). Cisplatin was the most common agent used in the concurrent setting. A total of 75 patients were treated with concurrent chemoradiation of which most patients (79%) received a total of 2 cycles of cisplatin while 17% of patients received cisplatin weekly followed by a median of 4 (IQR4-6) adjuvant chemotherapy cycles.

Adjuvant radiotherapy was delivered using EBRT with or without BT. Among the entire patient cohort, 120 (32%) received EBRT alone while 258 (68%) received EBRT and BT. The median EBRT dose was 45Gy (range 41.4-58Gy) delivered in 25 (range 23-31) fractions. The median dose of intracavitary BT was 12 Gy (range 5-25 Gy) in 2 (range 1-6) fractions. A majority of patients were treated with pelvic RT (n=286, 76%) while a smaller number of patients were treated with prophylactic PALN RT field (n=92, 24%).

Treatment outcomes and prognostic factors

The median follow-up was 45.8 months (IQR, 23 – 74 months) for the entire cohort. The estimated overall survival and recurrence-free survival rates at 5 years were 80% and 69%, respectively, for the entire cohort. There was no difference in the 5-year OS (77% vs. 87%, p=0.47) and RFS rates (67% vs. 70%, p=0.78) between patients treated with pelvic RT and those with prophylactic PA RT field, respectively as shown in Figure 2A and 2B. Among patients with endometrioid histology, there was no difference in the 5-year OS (86% vs. 88%, p=0.7) and RFS rates (74.5% vs. 77%, p=0.9) between patients treated with pelvic RT and those with prophylactic PALN RT field, respectively. Similarly among patients with non-endometrioid histology, there was no difference in the 5-year OS (60% vs. 70%, p=0.4) and RFS rates (51% vs. 31%, p=0.45).

When comparing 171 patients (45%) with PALN sampling and 207 patients (55%) with only pelvic lymph node dissection, women who had PALN sampling were more likely to get pelvic RT (82.5%) compared to those who did not have PALN sampling (70%), p=0.005. However, PALN sampling was not associated with OS or RFS ($p > 0.05$). In subgroup analysis of patients without PALN sampling, there was no difference in the 5-year OS (80% vs. 82%, p=0.63) between patients treated with pelvic RT and those treated with prophylactic PA RT field (Table 3). On univariate analysis for OS, age, race, depth of myometrial invasion, LVSI, number of positive pelvic nodes, type of radiation delivered (EBRT vs EBRT + BT) and chemoradiotherapy sequencing approach were not associated with overall survival ($p \geq 0.05$). Non-endometrioid histology ($p<0.001$), grade 3 ($p<0.001$), presence of adnexal (p=0.001) and cervical involvement

(p=0.008) were associated with worse OS. As for the extent of radiation field, no difference in OS was seen between patients treated with prophylactic PALN RT field vs. pelvic (p=0.50) (Table 4). On multivariate analysis, grade 3 (p = <0.001) and presence of adnexal involvement (p = 0.003) were significantly associated with worse OS (Table 5).

On univariate analysis for RFS, race (p=0.06), the number of positive pelvic lymph nodes (p=0.26), type of radiation delivered (EBRT vs EBRT +BT) (p=0.83) and chemoradiotherapy sequencing approaches (p=0.24) were not associated with RFS. Age ≥60 (p=0.02), non-endometrioid histology (p<0.001), grade 3 (p<0.001), myometrial invasion >50% (p=0.03), presence of LVSI (p=0.01), adnexal (p=0.001) and cervical involvement (p=0.001) were significantly associated with worse RFS. The extent of radiation field was not associated with RFS (p=0.78) (Table 4). On multivariate analysis, grade 3 (p < 0.001) and presence of adnexal involvement (p=0.007) were significantly associated with worse RFS (Table 5).

After propensity score matching, the estimated Hazard Ratios (HR) of prophylactic PALN RT field vs. pelvic RT field were 1.50 (95% CI = (0.71, 3.19), p-value = 0.28) for OS and 1.24 (95% CI = (0.64, 2.42), p-value = 0.51) for RFS, indicating that there was not enough evidence showing prophylactic PALN RT field associated with improved survival outcomes (Figure 2C, 2D).

Patterns of failure

A total of 100 (26%) patients had disease recurrence, among which 75 had received pelvic RT and 25 had received prophylactic PALN RT field. Distant recurrence was the most

common site of first recurrence (18.1% vs. 18.5%), followed by PALN (4.5% vs. 3.3%), pelvic LN only (1.4% vs. 3.3%), vagina only (1.4% vs. 1.1%) and pelvic LN with vagina (0.7% vs. 1.1%) in patients who received pelvic RT and those who received prophylactic PALN RT field, respectively (Table 6). EBRT field was not associated with the site of first recurrence (P=0.79). A total of 16 patients (4.2%) had isolated para-aortic relapses, among which 13 had received pelvic RT and 3 had received prophylactic PALN RT field. Among these 16 isolated PALN recurrences, 11 patients (69%) had age > 60 years, 11 (69%) endometrioid histology, 11 (69%) grade 3 tumor, 13 (81%) deep myometrial invasion, 15 (94.8%) presence of LVSI, 3 (19%) adnexal involvement, 7 (44%) cervical involvement, 12 (75%) EBRT + BT, 13 (81%) pelvic RT, 8 (50%) upfront chemotherapy and 6 (37.5%) "sandwich" chemotherapy.

Discussion

After extensive literature search, we believe that this is the largest study to evaluate the role of prophylactic PALN irradiation in women with stage IIIC1 EC who were treated with combined modality therapy including chemotherapy and radiation therapy. In our study and in agreement with other investigators [18, 19], prophylactic PALN RT did not statistically improve recurrence-free and overall survival in women with stage IIIC1 endometrial carcinoma who received adjuvant chemotherapy and RT.

In our study only 45% of patients had PALN sampling while 55% had only pelvic lymph node dissection, reflecting the lack of strong guidelines for PALN assessment. PALN sampling was recommended for macroscopic positive pelvic nodes or para-aortic nodes, or both as per

PORTEC 3, while pelvic lymph node sampling and para-aortic lymph node sampling were left optional as per GOG 258 [5-7]. The results of our study reflect the current practice across the United States and Canada, where PALN sampling is not systematically performed and prophylactic PALN RT is delivered at the discretion of the treating radiation oncologist. PALN irradiation was likely deemed unnecessary in patients who had negative PALN sampling, reflected by higher proportion of women with PALN sampling treated with pelvic RT (82.5%) compared to those without PALN sampling (70%). However, neither PALN sampling nor extent of radiation field was associated with OS or RFS.

On multivariate analysis, tumor grade and adnexal involvement were the only significant predictors of OS and RFS. Histology was not a significant predictor of OS and RFS on multivariate analysis, as detecting statistical significance is challenging given that an overwhelming majority of histology consisted of endometrioid (72.2%) vs. non-endometrioid (27.8%) in this study. Distant recurrence remains the most common site of first recurrence both in patients treated with pelvic RT and prophylactic PALN RT field. The patterns of failure were not correlated with the radiation treatment fields or chemoradiotherapy sequencing approaches.

Based on randomized trials including phase 3 trials demonstrating survival benefit with systemic chemotherapy [5-7, 20, 21], combined chemotherapy and radiotherapy forms the established framework of adjuvant therapy in the current treatment guidelines [15, 16, 22]. While the use of adjuvant chemoradiation has become a routine practice, there is a lack of consensus regarding the details on radiation target volume, and therefore the ideal RT target

remains controversial especially in the setting of positive pelvic lymph node EC without PALN involvement. This study evaluates the role of prophylactic PALN radiation therapy in stage IIIC1 EC. The 5-year overall survival and recurrence-free survival for stage IIIC disease varies between 60-90% and 59-80%, respectively [5, 7, 20, 21, 23-26]. Differences in survival outcomes across the studies are mainly due to variations in patient selection and treatment modalities. Meanwhile, there are fewer studies reporting survival outcomes of stage IIIC1 specifically, and these retrospective studies reported 5-year survival estimates as high as 85.7% [23] and as low as 23% for IIIC1 disease with multitude of comorbidities [27].

The large randomized phase III PORTEC-3 trial included 686 high-risk EC patients and reported 5-year OS of 78.7% and failure-free survival of 69.3% in subgroup analysis of stage III patients [5]. The 5-year OS of 80% and RFS of 69% in our study are very comparable to the survival outcomes of PORTEC-3 trial [5]. Another large randomized phase III GOG 258 trial reported a lower 5-year relapse-free survival of 59% possibly due to inclusion of larger proportion of stage IIIC patients who may have an inherently higher risk of local relapse compared to other high-risk stage I-II patients [7]. While the historical Surveillance, Epidemiology, and End Results (SEER) analysis using the database from 1988 to 2001 showed 60% survival rate among women with stage III EC (2009 FIGO staging) [25], the updated analysis using the more recent SEER database from 2004 to 2012 reported the 3-year OS of 80.5% [26], which again is very comparable to the 5-year OS of 80% in our study. The steep rise of the survival outcomes observed in the more recent analysis may be due to improved treatment modalities including introduction of chemotherapy and advancement of radiation techniques.

The standard extended-field radiotherapy is defined as the pelvic volume plus the entire common iliac chain and PALN region [22]. Although studies have shown the benefit of extended-field radiotherapy in decreasing PALN failure [28, 29] and improving overall survival and distant metastasis [30] in the setting of cervical cancer, the benefit appears less robust for endometrial carcinoma. On one hand, the National Comprehensive Cancer Network guidelines recommend the upper border of the extended field cover at least 1-2 cm above the level of the renal vessels, though it suggests that the ultimate RT volume be determined at the discretion of the treating physician depending on the clinical situation [22]. On the other hand, the RTOG 2021 consensus guidelines recommends coverage of the PALN chain when there is pathologic or radiographic evidence of PALN involvement or substantial risk of microscopic disease is suspected by the clinician with moderate agreement for para-aortic nodal CTV with the upper border covering 1 to 1.5 cm above the left renal vessels [31]. In summary, data on the volume of prophylactic PALN RT field may vary without substantial agreement for para-aortic nodal volume by experts [22, 31]. Furthermore, prophylactic PALN RT field is known to be associated with higher toxicities, especially acute gastrointestinal and hematologic toxicities [32], hence it is not routinely delivered in the prophylactic setting. Therefore, institutional variations and clinician preferences ultimately dictate the radiation treatment fields.

To our knowledge, there is no prospective data and few retrospective studies comparing the treatment fields for clinical outcomes in patients with stage IIIC1 disease. Our study did not report a correlation between treatment field extent and survival outcomes. Patterns of failure were similar for pelvic and prophylactic PALN RT field, and distant metastases remains the

dominant pattern of first recurrence. Similarly, Onal et al. reported no significant difference between pelvic RT and prophylactic PALN RT field in terms of overall survival, progression-free survival and patterns of failure in a cohort of 167 women with stage IIIC1 disease who were treated with either adjuvant RT to the pelvis (64%) or to the pelvis and PALN (36%) with or without systemic chemotherapy [18]. The latter study also showed that patients who received pelvic RT with chemotherapy had better OS and PFS compared to those who received pelvic and prophylactic extended PALN field without chemotherapy and concluded that prophylactic PALN RT field is unnecessary, even if chemotherapy is used together with pelvic-RT [18]. However, our study differed from that of Onal et al. in that all patients in our study cohort received adjuvant chemotherapy. While 80% of patients received adjuvant chemotherapy in Onal's study cohort, the proportion of patients receiving chemotherapy was significantly higher among patients treated with pelvic RT compared to those treated with prophylactic PALN RT field (67% vs. 33%, p = 0.05) [18]. Propensity matching was performed in both our study and Onal study, and subgroup analysis of matched cohort in Onal study showed no difference in the 5-year OS and RFS between pelvic RT and prophylactic PALN RT in patients treated with or without chemotherapy [18].

A similar study by Holloway et al. reported a higher 5-year OS in patients treated with prophylactic PALN RT field compared to pelvic RT (79.1% vs. 47.0%, P=0.01) among 57 women with EC with N1-only involvement who were treated with either adjuvant pelvic RT (40%) or prophylactic PALN RT field (60%) [19]. On multivariate analysis, however, radiation therapy volume was not significantly associated with survival [19]. In addition, despite the observed

trend for lower recurrence rates in those who received prophylactic PALN RT field (26 % vs. 52%, P=0.06), the vast majority of first recurrences occurred at distant sites in both groups, and there were no isolated PALN recurrences even among those who did not receive prophylactic PALN RT field [19]. Similarly, in our study, distant recurrence was the most common site of first recurrence both in patients treated with pelvic RT and prophylactic PALN RT field, followed by PALN with or without pelvis, pelvis only, vagina only, and pelvis with vagina. The patterns of failure found by Holloway et al. and our study are consistent with the results of other studies prospective and randomized that found that the majority of recurrences in women with stage IIIC endometrial cancer typically occur at distant sites [6, 7, 24, 33, 34].

In contrast to these findings, Lee et al. reported that the most common site of recurrence in patients treated with pelvic RT was the para-aortic chain (12%) followed by distant recurrence and pelvis, while the most common site of recurrence in patients treated with prophylactic PALN RT field was distant recurrence followed by para-aortic chain and pelvis [35]. The latter study has several limitations including the small number of patients in this subset and the failure to detect if chemotherapy reduced the risk of PALN failure when pelvic RT was delivered [35]. Furthermore, only 67% of patients received adjuvant chemotherapy and the proportion of patients receiving chemotherapy in respective radiation fields – pelvic RT, prophylactic PA RT field, and whole-abdominal RT - was unknown in Lee's study [35]. Unlike these prior studies that included patients who received various types of adjuvant therapy [18, 19, 35], our study is unique in examining only patients treated with combined adjuvant

chemoradiation therapy such that the presence or absence of chemotherapy is not a confounding factor.

We acknowledge that our study has several limitations. First, it is a retrospective study with inherent selection and information biases. A small proportion of patients was treated with prophylactic PALN RT field which reflects the current practice and lack of consensus on the extent of radiation fields for locally advanced EC with positive pelvic nodes. While most variables were balanced between the 2 treatment groups, there were significantly more favorable grade and histology in the PALN RT group. Treatment-related toxicities were not reported due to the limited data available and the grading heterogeneity across the 13 participating centers. Prophylactic PALN RT field is known to be associated with higher toxicities mainly gastrointestinal and hematologic [32, 36], which is the major drawback of its routine use. Assessment of acute and chronic toxicities may have served as valuable information to further evaluate the risks and benefits of the prophylactic PALN RT field. Furthermore, the sequencing of chemotherapy also varied including upfront chemo, concurrent and “sandwich” regimen, and upfront RT. In our previous publication, sequencing approaches of chemoradiotherapy did not impact survival outcomes [37]. Despite these limitations, our study provides valuable outcomes data on the effects of prophylactic PALN RT in patients with nodal involvement limited to the pelvis. In the few studies that stratified the results in stage IIIC1 vs. IIIC2, the results are based on smaller patient sample sizes (n<60) [17, 19, 23, 38], illustrating the value of our large study that consists of 378 stage IIIC1 patients. To our knowledge, our study is the largest retrospective series available at this time that evaluates the role of radiation treatment

volume on the clinical outcomes and the patterns of failure among patients with stage IIIC1 endometrial carcinoma which could impact clinical practice by helping clinicians in decision-making.

Conclusion

In this multi-institutional analysis of women with stage IIIC1 endometrial cancer, prophylactic PALN RT field was not significantly associated with improved survival outcomes. Distant recurrence was the most common site of failure both in patients treated with pelvic RT and prophylactic PALN RT field. This study suggests that prophylactic PALN RT field is not warranted in the setting of pelvic lymph node positive EC without PALN involvement. As distant metastasis remains the most site of failure despite routine use of systemic chemotherapy, new therapeutic approaches including molecular markers are necessary to optimize the outcomes for women with stage IIIC1 endometrial cancer.

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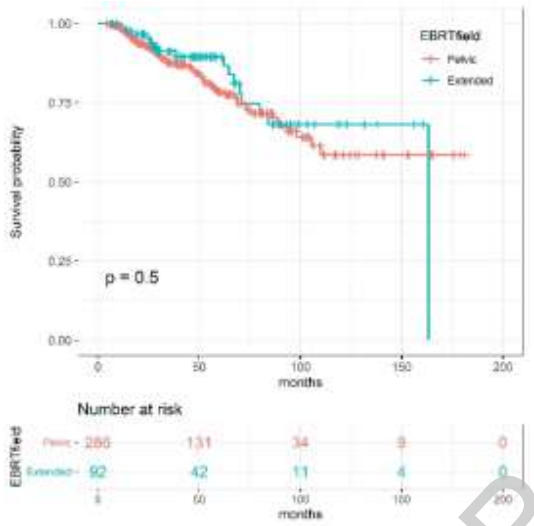
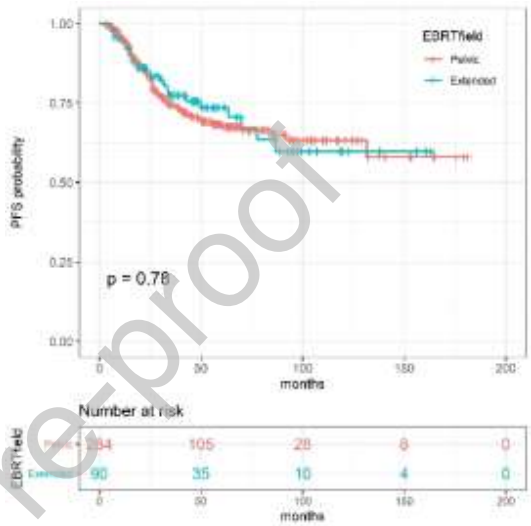
Figure 1. The Kaplan-Meier estimate curves for (A) OS and (B) RFS for Pelvic RT and prophylactic PALN RT in the entire cohort. The (C) OS and (D) RFS for pelvic RT and prophylactic PALN RT field in the matched cohort.



A.



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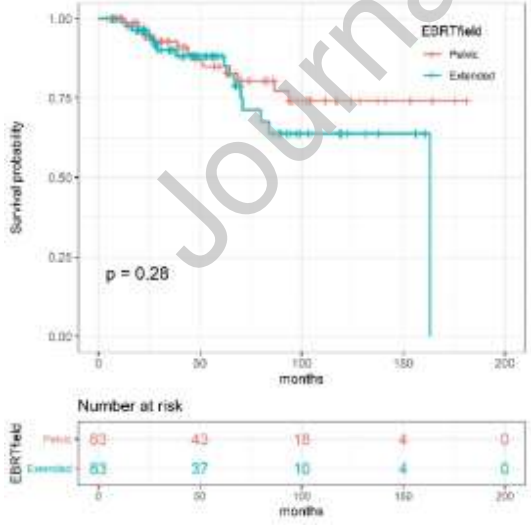

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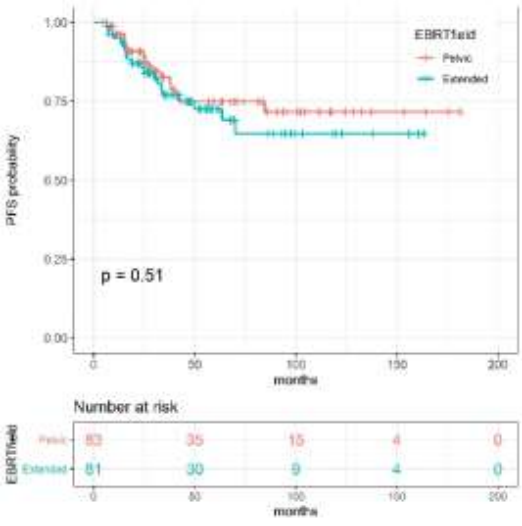

D.

Table 1. Patient characteristics and risk factors according to the extent of the radiation field in the entire cohort

Characteristics	Entire cohort n=378 (%)	Pelvic RT, n=286 (%)	Pelvic + prophylactic PA field RT, n=92 (%)	P-value
Median age (years)	62 (IQR 55-69)	62 (IQR 55-70)	62 (IQR 54-67)	
Age				
< 60	165 (44%)	121 (42%)	44 (48%)	0.42
≥ 60	213 (56%)	165 (58%)	48 (52%)	
Median number of pelvic LN +	2 (IQR 1-2)	2 (IQR 1-2)	2 (IQR 1-2)	
Median number of LN resected	14 (IQR 9-21)	15 (IQR 10-22)	12 (IQR 8-17)	
Positive LN				
1	186 (49%)	146 (51%)	40 (43%)	0.25
≥ 2	192 (52%)	140 (49%)	52 (57%)	
Pathology				
Endometrioid	273 (72%)	197 (69%)	76 (83%)	0.02
Non-endometrioid	105 (28%)	89 (31%)	16 (17%)	
Grade				
I and II	196 (52%)	137 (48%)	59 (65%)	0.01
III	179 (48%)	147 (52%)	32 (35%)	
Depth of myometrial invasion				
< 50%	109 (29%)	82 (29%)	27 (29%)	1.00
≥ 50%	269 (71%)	204 (71%)	65 (71%)	
Adnexal involvement				
Absent	306 (83%)	237 (84%)	69 (80%)	0.51
Present	62 (17%)	45 (16%)	17 (20%)	
Cervical involvement				
Absent	238 (64%)	177 (62%)	61 (68%)	0.35
Present	135 (36%)	107 (38%)	28 (32%)	
Race				
Non-black	321 (88%)	240 (88%)	81 (90%)	0.67
Black	43 (12%)	34 (12%)	9 (10%)	
LVSI				
Absent	79 (21%)	61 (22%)	18 (20%)	0.84
Present	292 (79%)	220 (78%)	72 (80%)	
Type of RT				
EBRT alone	120 (32%)	106 (37%)	14 (15%)	< .001
EBRT + BT	258 (68%)	180 (63%)	78 (85%)	
Treatment sequencing				
Upfront CHT	178 (47%)	117 (41%)	61 (66%)	
Concurrent CHT	75 (20%)	60 (21%)	15 (16%)	< .001
“Sandwich” method	106 (28%)	96 (34%)	10 (11%)	
Upfront RT	19 (5%)	13 (4%)	6 (7%)	

LN: lymph node; IQR: interquartile range; LVSI: lymphovascular space invasion; PA: para-aortic; RT: radiotherapy; EBRT: external beam radiotherapy; CHT: chemotherapy; “Sandwich” method: initial chemotherapy of limited duration, followed by radiotherapy, and then subsequent consolidation chemotherapy again.

Table 2. Patient characteristics and risk factors according to the extent of the radiation field in the matched cohort

Characteristics	Entire cohort n=166 (%)	Pelvic RT, n=83 (%)	Pelvic + prophylactic PA field RT, n=83 (%)	P-value
Median age (years)	61 (IQR 54-68)	61 (IQR 54-68)	61 (IQR 54-67)	
Age				
< 60	78 (47%)	38 (46%)	40 (48%)	0.88
≥ 60	88 (53%)	45 (54%)	43 (52%)	
Median number of pelvic LN +	2 (IQR 1-3)	2 (IQR 1-3)	2 (IQR 1-3)	
Positive LN				
1	77 (46%)	39 (47%)	38 (46%)	1.00
≥ 2	89 (54%)	44 (53%)	45 (54%)	
Pathology				
Endometrioid	140 (84%)	71 (86%)	69 (83%)	0.83
Non-endometrioid	26 (16%)	12 (15%)	14 (17%)	
Grade				
I and II	101 (61%)	48 (58%)	53 (65%)	0.46
III	64 (39%)	35 (42%)	29 (35%)	
Depth of myometrial invasion				
< 50%	57 (34%)	31 (37%)	26 (31%)	0.51
≥ 50%	109 (66%)	52 (63%)	57 (69%)	
Adnexal involvement				
Absent	135 (81%)	68 (82%)	67 (81%)	1.00
Present	31 (19%)	15 (18%)	16 (19%)	
Cervical involvement				
Absent	116 (70%)	57 (69%)	59 (71%)	0.87
Present	50 (30%)	26 (31%)	24 (29%)	
Race				
Non-black	150 (90%)	76 (92%)	74 (89%)	0.79
Black	16 (10%)	7 (8%)	9 (11%)	
LVSI				
Absent	34 (21%)	16 (19%)	18 (22%)	0.85
Present	132 (79%)	67 (81%)	65 (78%)	
Type of RT				
EBRT alone	22 (13%)	11 (13%)	11 (13%)	1.00
EBRT + BT	144 (87%)	72 (87%)	72 (87%)	
Treatment sequencing				
Upfront CHT	118 (71%)	60 (72%)	58 (70%)	
Concurrent CHT	22 (13%)	10 (12%)	12 (14%)	0.94
“Sandwich” method	17 (10%)	9 (11%)	8 (10%)	
Upfront RT	9 (5%)	4 (5%)	5 (6%)	

LN: lymph node; IQR: interquartile range; LVSI: lymphovascular space invasion; PA: para-aortic; RT: radiotherapy; EBRT: external beam radiotherapy; CHT: chemotherapy; "Sandwich" method: initial chemotherapy of limited duration, followed by radiotherapy, and then subsequent consolidation chemotherapy again.

Table 3: Extent of radiation field by para-aortic lymph node sampling

	Pelvic RT	Prophylactic PA RT
No PALN Sampling (n=206)	144 (70%)	62 (30%)
PALN Sampling (n=171)	141 (83%)	30 (17%)
Total (n=377)	285 (76%)	92 (24%)

PA: para-aortic; PALN: para-aortic lymph node; RT: radiotherapy

Table 4. Univariate analysis of prognostic factors for overall survival and recurrence-free survival

Variables	HR (95% CI)	P-value
Overall survival		
Age ≥ 60 vs. < 60	1.42 (0.88-2.27)	0.15
Race black vs. other	1.83 (0.98-3.40)	0.06
Myometrial invasion ≥ 50% vs. < 50%	1.76 (0.98-3.16)	0.06
LVSI present vs. absent	1.86 (0.92-3.74)	0.08
Number of pelvic LN+ ≥ 2 vs. 1	1.60 (1.00-2.55)	0.05
Type of RT EBRT vs. EBRT + BT	0.94 (0.57-1.55)	0.80
Treatment sequencing		0.54
Upfront chemo vs. concurrent	1.24 (0.64-2.42)	
Upfront chemo vs. sandwich	1.50 (0.87-2.61)	
Upfront chemo vs. upfront RT	1.33 (0.56-3.18)	
Histology non-endometrioid vs. endometrioid	2.59 (1.63-4.10)	<0.001
Grade 3 vs. 1-2	3.05 (1.85-5.03)	<0.001
Adnexal involvement present vs. absent	2.38 (1.45-3.88)	0.001
Cervical involvement present vs. absent	1.87 (1.18-2.98)	0.008
Field of RT PALN prophylactic vs. pelvic	0.83 (0.47-1.44)	0.50
Recurrence-free survival		
Age ≥60 vs. <60	1.64 (1.08-2.48)	0.02

Race black vs. other	1.67 (0.98-2.87)	0.06
Myometrial invasion ≥ 50% vs. < 50%	1.72 (1.05-2.81)	0.03
LVSI present vs. absent	2.45 (1.27-4.73)	0.01
Number of pelvic LN+ ≥ 2 vs. 1	1.26 (0.85-1.88)	0.26
Type of RT EBRT vs. EBRT + BT	1.05 (0.68-1.63)	0.83
Treatment sequencing		0.24
Upfront chemo vs. concurrent	1.15 (0.66-2.03)	
Upfront chemo vs. sandwich	1.63 (1.03-2.58)	
Upfront chemo vs. upfront RT	1.31 (0.55-3.08)	
Histology non- endometrioid vs endometrioid	2.28 (1.53-3.40)	<0.001
Grade 3 vs. 1-2	3.36 (2.18-5.20)	<0.001
Adnexal involvement present vs. absent	2.15 (1.39-3.33)	0.001
Cervical involvement present vs. absent	1.92 (1.28-2.87)	0.001
Field of RT PALN prophylactic vs. pelvic	0.94 (0.59-1.49)	0.78

LVSI: lymphovascular space invasion; LN: lymph node; PALN: para-aortic lymph node; RT: radiotherapy; EBRT: external beam radiotherapy; BT: brachytherapy; "Sandwich": initial chemotherapy of limited duration, followed by radiotherapy, and then subsequent consolidation chemotherapy again.

Table 5. Multivariate analysis of prognostic factors for overall survival and recurrence-free survival

Variables	HR (95% CI)	P-value
Overall survival		
Age ≥ 60 vs. < 60	1.50 (0.91-2.49)	0.11
Myometrial invasion ≥ 50% vs. < 50%	1.49 (0.82-2.70)	0.19
Positive LN ≥ 2 vs. 1	1.39 (0.86-2.27)	0.18
Grade 3 vs. 1-2	2.59 (1.54-4.36)	<0.001
Adnexal involvement present vs. absent	2.19 (1.30-3.69)	0.003
Cervical involvement present vs. absent	1.38 (0.84-2.27)	0.21
Recurrence-free survival		
Age ≥ 60 vs. < 60	1.53 (0.99-2.36)	0.06
LVSI present vs. absent	2.04 (1.02-4.09)	0.05
Grade 3 vs. 1-2	3.00 (1.90-4.76)	<0.001
Adnexal involvement present vs. absent	1.87 (1.19-2.96)	0.007

LN: lymph node; LVSI: lymphovascular space invasion.