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Combined Chemotherapy and Radiation Improves Survival for Node-Positive Endometrial Cancer

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Abstract

Objective—To evaluate the clinical outcomes for women with node-positive endometrioid adenocarcinoma of the uterus

Methods—Records were reviewed for 66 patients with Stage IIIC endometrioid adenocarcinoma diagnosed between 1/1995 and 12/2009. Study inclusion required TAH, BSO and negative chest imaging. Papillary serous and clear cell histologies were excluded. Adjuvant treatment was external beam radiation (RT) alone in 18 patients (27%), combined chemotherapy and RT in 44 (67%), chemotherapy alone in 1 (2%), and no adjuvant therapy in 3 (5%). The median follow-up was 48 months.

Results—Of 66 patients, 56 (85%) had positive pelvic nodes only, 5 (8%) had positive para-aortic nodes only, and 5 (8%) had both. Of the 62 patients who received adjuvant RT, only 4 (6%) had an in-field recurrence, including 2 with residual disease after surgery. Disease-free (DFS) and overall (OS) survival rates at 5 years were 71% and 81%, respectively. By adjuvant treatment modality, 5-year DFS and OS rates were 63% and 67% for RT alone and 79% and 90% for combined modality therapy ($p=0.15$ and $p<0.01$). On multivariate analysis, combined modality therapy significantly improved DFS (HR 0.12, 95% CI 0.03–0.49, $p<0.01$) and OS (HR 0.20, 95% CI 0.05–0.75, $p=0.02$) compared to adjuvant RT alone.

Conclusions—Compared to RT alone, combined modality therapy decreased recurrence and improved survival in patients with node-positive endometrioid adenocarcinoma of the uterus. In addition, external beam RT resulted in excellent local and regional control. Future studies are needed to define the optimal chemotherapy regimen, sequencing, and radiation fields.

Keywords

(5) FIGO IIIC endometrial cancer; node-positive endometrial cancer; radiation therapy; endometrioid histology

Background

Surgery or pathologic evaluation reveals that 5–20% of patients with endometrial cancer have pelvic and/or para-aortic nodal involvement at presentation.^{1–3} Nodal metastases can occur at any level within the pelvis or para-aortic chain due to the rich lymphatic network of the uterus, and the risk of lymph node involvement increases with the depth of myometrial invasion, high tumor grade, presence of lymphovascular invasion and intraperitoneal disease. In a surgical staging study from the Gynecologic Oncology Group (GOG), the

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incidence of pelvic and para-aortic nodal involvement was 18% and 15%, respectively, in patients with deep myometrial invasion, and 33% and 8% in those with intraperitoneal disease.¹ The presence of both risk factors increased the incidence of nodal involvement to 61% for pelvic nodes and 30% for para-aortic nodes.

FIGO (International Federation of Obstetrics and Gynecology) Stage III disease describes a heterogeneous group of patients with regional tumor spread involving the uterine serosa or adnexa (IIIA), metastasis to the vagina (IIIB), or spread to the pelvic (IIIC1) and/or para-aortic (IIIC2) lymph nodes.⁴ Despite the clinical heterogeneity of Stage III endometrial cancer, randomized studies of adjuvant therapy have routinely included patients with advanced stage disease as well as those with various histologic subtypes, including uterine papillary serous and clear cell carcinoma. Given the various disease presentations and biologic subtypes, it is unclear if adjuvant therapy recommendations should be tailored to specific subgroups, as subset analysis from randomized data has been limited due to small patient numbers. There is currently no clear consensus on the use of adjuvant chemotherapy and/or radiotherapy (RT) for Stage III endometrial cancer, although involved field RT may benefit patients with regional nodal spread given the high local recurrences rates. Retrospective studies have reported 5-year survival rates of 50–70% after adjuvant RT,^{5–8} and up to 80% with combined modality therapy.⁹

At our institution, patients with Stage IIIC endometrial cancer routinely receive postoperative RT with or without chemotherapy to reduce the risk of pelvic and regional recurrence. The primary aim of this study is to evaluate clinical outcomes by adjuvant therapy type in patients with node-positive endometrial cancer. In addition, we identify prognostic factors for recurrence and survival and describe the patterns of treatment failure following observation, chemotherapy alone, RT alone and combined chemotherapy and RT.

Methods

A review of the clinical databases at Brigham and Women's Hospital and Dana-Farber Cancer Institute identified 70 women with FIGO Stage IIIC endometrioid (non-serous, non-clear cell) adenocarcinoma of the uterus diagnosed between January 1, 1995 and December 31, 2009. With the approval of the Institutional Review Board, clinical data were abstracted from the medical record, including review of operative notes, pathology reports, the radiotherapy record and clinic notes. Four patients had no follow-up after surgery and were excluded from the study. The remaining 66 patients constitute the study population.

Patients and treatment

All 66 patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with negative omental biopsy. Pelvic lymph node assessment included sampling in 20 patients (30%) and dissection in 46 (70%). The para-aortic lymph nodes were removed in 15 patients (23%). One patient had gross residual disease in the pelvic and para-aortic nodal chain and 1 had residual parametrial disease. Chest imaging was negative in all patients.

Adjuvant treatment was external beam RT alone in 18 patients (27%), combined chemotherapy and RT in 44 (67%), chemotherapy alone in 1 (2%), and no adjuvant therapy in 3 (5%). In the observation group, all 3 patients were seen in consultation by a medical oncologist and a radiation oncologist and declined adjuvant therapy. The use of combined modality therapy became more common in the later treatment years; the proportion of patients treated with both chemotherapy and RT increased from 45% in the years 1995–1999 to 73% in 2000–2009. The selection of the RT field and boost volumes was determined by the radiation oncologist. The RT field included the pelvis in 41 patients, pelvis and para-

aortic lymph nodes (extended field RT) in 15 and the whole abdomen in 6. Thirty-six of 41 patients treated with pelvic RT did not have sampling of the para-aortic lymph nodes and 5 had pathologically negative para-aortic nodes. Among the 15 patients treated with extended field RT, 6 had positive para-aortic lymph nodes and 9 did not have para-aortic sampling and were treated prophylactically. Among the 6 patients who received whole abdominal RT, 3 had positive para-aortic nodes and 3 did not have the para-aortics assessed surgically. The indication for whole abdominal RT was positive cytology in 5 patients. The median dose for pelvic RT was 45 Gy (range, 30.6–54 Gy), with a cone-down dose of 5.4–9 Gy in 7 patients. The median dose to the para-aortic lymph nodes was 45 Gy (range, 40–50.4 Gy); 8 patients treated with extended field RT received a pelvic cone-down dose of 5.4–18 Gy. The median dose for whole abdominal RT was 30 Gy with a pelvic boost to 45 Gy. Of these 6 patients, a para-aortic nodal boost to 45 Gy was delivered in 2 patients and a pelvic boost of 5.4 Gy was given in 1 patient. A vaginal boost was delivered by high-dose-rate brachytherapy in 47 patients (median dose, 16 Gy) and by low-dose-rate brachytherapy in 1 patient (19.4 Gy).

Adjuvant chemotherapy was delivered in 45 patients (68%) with a median of 3 cycles (range, 3–6 cycles). Thirty-six patients received carboplatin and paclitaxel prior to adjuvant RT, and 5 were treated with paclitaxel, doxorubicin, and cyclophosphamide (TAC). Less frequently used regimens included cisplatin and doxorubicin in 2 patients, cisplatin and paclitaxel in 1 patient, and concurrent cisplatin and RT followed by carboplatin and paclitaxel in 1 patient. Two patients received adjuvant hormonal therapy, including anastrozole following TAC chemotherapy and megestrol acetate following pelvic RT.

Patients were seen in routine follow-up every 3 months for 2 years after the completion of therapy, and every 6 months thereafter according to institutional practice. Follow-up visits included an interval history, physical examination and Pap smear of the vaginal vault. Surveillance chest, abdominal and pelvic CT scans were performed at the discretion of the medical oncologist. The site or sites of recurrent disease were documented following re-staging chest, abdominal and pelvic CT scans. Distant metastatic disease was considered extra-abdominal and most commonly involved the mediastinum, supraclavicular lymph nodes, and lungs. Recurrent disease was also categorized as in-field or out-of-field based on the RT field.

Statistical analysis

Clinical, pathologic, and treatment characteristics were compared for patients treated with RT alone and those treated with combined chemotherapy and RT using the Wilcoxon rank sum, chi-squared approximation, or Fisher exact test. The following covariates were analyzed to identify predictors of disease-free and overall survival: age, tumor grade, presence of lymphovascular invasion, depth of myometrial invasion, cervical involvement, positive peritoneal cytology, adnexal involvement, extent of lymph node surgery (sampling or dissection), para-aortic sampling, number of recovered lymph nodes, number of positive lymph nodes, site of nodal involvement (pelvic or para-aortic), RT type (pelvic, extended field or whole abdomen), and adjuvant treatment modality. Actuarial estimates of disease-free (DFS) and overall (OS) survival were determined using the Kaplan-Meier method. Survival estimates were not calculated for the patients who received chemotherapy alone or no adjuvant therapy given the small number of patients. DFS was defined as the interval from the date of diagnosis until the date of first recurrence or death of any cause. Overall survival was calculated from the date of diagnosis until death from any cause as determined from the medical record or the Social Security Death Index. Survival time was calculated at the date of last follow-up for censored patients. Survival curves for categorical covariates were compared by the logrank test. The univariate Cox proportional hazards model was used to analyze the covariates. Multivariate analysis was performed using the Cox proportional hazards model to identify independent predictors of DFS and OS using a backward stepwise

regression method. Statistical analysis was performed using the statistical software JMP, v. 8.0.1 (SAS Institute). Statistical tests were two-sided and considered significant for p-values less than 0.05.

Results

The median age at diagnosis was 59 years (range, 33–77 years) and median tumor size was 4 cm (range, 2–12 cm). The baseline clinical and pathologic characteristics for the entire cohort of 66 patients are shown in Table 1, and are compared for women who received adjuvant RT and those who received both chemotherapy and RT. Women who received combined modality therapy were significantly younger (58 vs. 63 years, $p=0.04$) and had higher rates of adnexal involvement (37% vs. 6%, $p=0.01$). Although the number of recovered lymph nodes was similar, women who received adjuvant chemotherapy and RT had a greater number of positive lymph nodes (2 vs. 1, $p=0.02$).

Clinical outcomes and prognostic factors

The median follow-up time was 48 months (range, 8–160 months). DFS and OS rates at 5 years were 71% and 81%, respectively. The unadjusted hazard ratios for the univariate analysis are summarized in Table 2. Tumor grade was not independently prognostic for recurrence ($p=0.09$) or survival ($p=0.4$). The DFS estimates by tumor grade are shown in Figure 1. In addition, the presence of lymphovascular invasion was not significantly associated with DFS ($p=0.10$) or OS ($p=0.3$). Outcomes were not significantly different between patients with deep myometrial invasion ($\geq 50\%$) and those with $<50\%$ invasion ($p=0.09$ for DFS and $p=0.18$ for OS). Furthermore, adnexal involvement and positive peritoneal cytology were not prognostic for DFS or OS (all $p>0.4$). In contrast, patients with cervical stromal involvement had significantly worse outcomes compared to patients with none ($p<0.01$ for DFS and $p=0.03$ for OS). Advancing age was also strongly negatively associated with recurrence (HR 1.07/year increase, $p<0.01$) and survival (HR 1.07/year, $p=0.01$). The extent of surgical staging, either pelvic lymph node dissection or sampling, was not related to recurrence or survival (all $p \geq 0.2$). Women with para-aortic nodal sampling ($n=15$) had similar recurrence and OS rates to those with none ($p=0.7$ for DFS and $p=0.14$ for OS). Clinical outcomes were also similar for patients with positive para-aortic nodes and those with positive pelvic nodes (all $p>0.2$). In addition, the total number of recovered nodes and number of positive nodes was not prognostic for outcome (all $p>0.2$).

Adjuvant treatment

Most patients (94%) received adjuvant radiotherapy, including combined chemotherapy and radiation in 44 (67%). One patient treated with chemotherapy alone had disease progression prior to initiation of RT. Three patients declined adjuvant chemotherapy and/or RT. By adjuvant treatment modality, DFS at 5 years was 63% for RT alone and 79% for combined modality therapy (Figure 2A, $p=0.15$). As shown in Figure 2B, OS differed significantly by adjuvant modality: 67% for RT alone and 90% for combined modality therapy ($p<0.01$). There was no survival difference by RT type, as DFS at 5 years was 68% for pelvic, 84% for extended field and 83% for whole abdominal RT ($p=0.97$). The use of brachytherapy was not associated with DFS ($p=0.3$) or OS ($p=0.8$).

On multivariate analysis, older age at diagnosis, deep myometrial invasion, and higher tumor grade predicted for lower DFS rates, while the use of both chemotherapy and RT was associated with improved DFS when compared to RT alone (Table 3). Independent predictors of lower OS rates were older age at diagnosis and cervical involvement, while the use of combined modality therapy predicted for improved OS rates when compared to RT alone.

Patterns of disease recurrence

Seventeen patients (26%) had disease recurrence a median of 21 months (range, 5- 71 months) after treatment. Of the 41 patients who received pelvic RT, 3 (7%) had an isolated para-aortic recurrence and 2 (5%) had recurrence in the para-aortics and mediastinal or supraclavicular nodes. The rates of para-aortic recurrence were similar in the patients who received chemotherapy and pelvic RT and in those who received pelvic RT alone (14% vs. 8%, respectively, $p=1.0$). There was a non-significant difference in para-aortic recurrence rates in patients with ovarian involvement compared to those with none (25% vs. 7%, $p=0.14$). As shown in Table 4, the most common site of failure in patients treated with pelvic RT was the para-aortic chain ($n=5$, 12%) followed by distant metastases ($n=3$, 7%). Most recurrences in patients who received extended field or whole abdominal RT had a distant component. Of the 62 patients who received adjuvant RT, 59 (95%) achieved pelvic control. In the 4 patients who did not receive RT, 3 of 3 failures involved the pelvis and/or para-aortic lymph nodes. Although 12 patients had positive peritoneal cytology and 22 had intraperitoneal disease at diagnosis, there were no documented peritoneal recurrences. Ten of 14 recurrences in patients who received adjuvant RT were outside the RT field. Only four patients (6%) had an in-field recurrence; 2 of these had residual disease after surgery. One patient with unresectable parametrial disease had a vaginal recurrence following pelvic RT and vaginal brachytherapy and 1 patient with residual pelvic and para-aortic involvement experienced in-field progression following 6 cycles of carboplatin and taxol and extended field RT. The cause of death was determined as progressive disease in 11 patients and was unknown in 2 patients.

Discussion

This study reports the clinical outcomes of 66 patients with node-positive endometrial cancer of endometrioid subtype treated at our institution between 1995 and 2009. Most patients had multiple intrauterine risk factors for relapse, including high tumor grade, deep myometrial invasion, and lymphovascular invasion. Despite the advanced stage of presentation, the 5-year disease-free survival rate was 71% and the overall survival rate was 80%. Based upon our institutional practice, adjuvant radiotherapy was delivered in 94% of patients; 3 patients declined adjuvant treatment and 1 patient experienced disease progression on chemotherapy. Although the number of patients is small, 3 of the 4 patients who did not receive RT relapsed.

This study primarily evaluates the importance of combined modality therapy in a cohort that largely received adjuvant RT. In this retrospective comparison, combined modality therapy decreased recurrence rates and improved survival despite more unfavorable pathologic factors in the women who received both chemotherapy and radiation, including higher rates of adnexal involvement and a greater number of positive lymph nodes. Patients who received both chemotherapy and RT were approximately 5 years younger than women treated with RT alone, although combined modality therapy retained its prognostic significance for recurrence and survival when adjusted for age. Klopp, *et al.* published a report of 71 women with node-positive endometrial cancer treated with regional RT or systemic therapy with 5-year survival rates of 73% for RT and 40% for chemotherapy alone.¹⁰ After a median follow up of 48 months, the 5-year overall survival rate in our series was 67% for adjuvant RT alone, comparable to the Klopp study, and 90% for combined modality therapy. Both of these large institutional series limited the analysis to patients with non-serous, non-clear cell histology, and demonstrated that patients with node-positive disease of the endometrioid subtype have excellent outcomes following regional RT. Other retrospective series in the literature report 5-year survival estimates of 46–84% for patients with Stage IIIC disease treated with postoperative RT.^{5,7–9,11} The reported 5-year survival

rates for patients with systemic pelvic and para-aortic lymphadenectomy treated with adjuvant chemotherapy range from 48–76%.^{12–14}

Several randomized trials have compared adjuvant chemotherapy to radiation therapy in patients with high risk or advanced stage disease. GOG 122 was a randomized trial of adjuvant whole abdominal radiotherapy versus doxorubicin-cisplatin chemotherapy in women with Stage III or IV endometrial cancer.¹⁵ Although the survival outcomes favored the chemotherapy arm, the study population was significantly heterogeneous in terms of clinical substage, histologic cell type and the extent of surgical debulking. The authors commented that whole abdominal RT may not have been the most effective approach for advanced stage disease, and suggested that tailored pelvic or pelvic and para-aortic RT with higher doses in conventional fractionation may improve the therapeutic ratio. A randomized trial from Italy compared pelvic radiotherapy and systemic chemotherapy in women with high risk disease and found no survival difference between the adjuvant treatment arms.¹⁶ However, pelvic relapses were more common in the chemotherapy group and distant relapses occurred more frequently after pelvic RT. Similarly, a randomized trial of women with intermediate and high risk endometrial cancer from Japan reported equivalent survival outcomes for adjuvant chemotherapy versus pelvic radiotherapy.¹⁷ A combined modality treatment approach showed significant promise in a phase II study from the Radiation Therapy Oncology Group (RTOG), with a 4-year survival rate of 77% for women with Stage III disease.¹⁸ With chemoradiotherapy, pelvic and regional recurrence rates were 2% and distant failure was 19%. More recently, a combined analysis of 2 randomized trials from Europe compared radiotherapy alone to combined modality therapy in a high risk and advanced stage population.¹⁹ The Nordic Society of Gynaecologic Oncology/European Organisation for the Research and Treatment of Cancer (Nordic/EORTC) trial predominately enrolled high risk, early stage patients, whereas the trial from the Mario Negri Institute (MaNGO ILIADE-III) contained a significant number of Stage III patients with non-clear cell, non-serous histology, including 81 with FIGO Stage IIIC disease. In the combined analysis, adjuvant chemotherapy and radiotherapy improved progression-free, but not overall, survival compared to radiotherapy alone, with the benefit limited to patients with endometrioid histology. The ongoing PORTEC-3 trial in high risk and advanced stage endometrial cancer will compare pelvic radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy based on the RTOG 9708 study described above. Given the survival benefit for adjuvant chemotherapy in GOG-122, a predecessor trial GOG-258 will evaluate combined modality therapy with involved-field radiotherapy versus adjuvant chemotherapy alone in high-risk and advanced stage disease. The combined modality therapy arm is also based on the RTOG 9708 paradigm.

Although randomized trials are underway to evaluate the role of combined modality therapy in high risk and advanced stage endometrial cancer, many questions will remain, such as the extent of surgical nodal staging, the sequencing of systemic therapy and the chemotherapeutic agents used, and the optimal radiation treatment volumes and dose. Systematic pelvic lymphadenectomy has been shown to lack a therapeutic benefit in patients with early stage endometrial cancer,^{20,21} although detection of nodal disease often guides treatment recommendations regarding the use of adjuvant RT and chemotherapy. The use of regional RT may include treatment volumes that cover the pelvis and/or para-aortic lymph nodes, and the optimal treatment field and dose have not yet been defined. Analysis of patterns of failure suggests that regional RT results in excellent in-field control of disease, and most recurrences are in the para-aortic nodes or a distant site. Para-aortic sampling was performed in just 15% of our patients, and detection of a positive node resulted in a recommendation for extended field RT in these patients. However, 36 patients received pelvic RT in the absence of para-aortic sampling, and 9 received prophylactic extended field RT. We observed a rate of para-aortic failure of 12% following pelvic RT and 7% following

extended field RT, comparable to other studies.¹⁰ When considering the patients treated with pelvic RT who did not have para-aortic sampling or dissection, the incidence of para-aortic relapse was 14%. Given the small number of patients in this subset, we were unable to detect if chemotherapy reduced the risk of para-aortic failure when pelvic radiotherapy was delivered. Given the concern for increased toxicity, our standard treatment recommendation for patients with limited pelvic nodal disease is adjuvant pelvic RT that encompasses the pelvic and common iliac lymph nodes.

In this retrospective study, the limitations of the treatment comparison include more frequent use of baseline and re-staging imaging studies in the later treatment years when combined modality therapy was more common, which could introduce a survival bias by excluding patients with metastatic disease. Nevertheless, most patients (56, 85%) in our study were treated after 2000 when CT imaging was routinely available. The use of PET for endometrial cancer staging has not been adopted at our institution due to its low sensitivity.²² Given the small numbers of patients treated with chemotherapy alone, our study is insufficiently powered to comment on the impact of chemotherapy alone, rather than combined modality therapy, on survival outcomes for stage IIIC disease. Nevertheless, we report a 5-year OS rate of 90% with both chemotherapy and RT, which suggests improved outcomes for combined modality therapy in stage IIIC disease.

In summary, adjuvant RT provided excellent local and regional control in patients with FIGO Stage IIIC endometrial cancer. Regional and distant recurrences outside the radiation field accounted for the majority of relapses. Despite pelvic and/or para-aortic nodal involvement, excellent survival rates may be achieved in patients with endometrioid tumors treated with adjuvant RT. However, new therapeutic approaches are necessary to increase survival rates for patients with node-positive disease, particularly those with high grade disease or risk factors such as deep invasion or cervical involvement.

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Figure 1.
DFS by tumor grade

Figure 2.
(A) DFS and (B) OS for combined chemotherapy and radiotherapy (chemoRT) and radiotherapy alone (RT)

Table 1

Clinical and pathologic characteristics of 66 patients with FIGO Stage IIIC endometrioid adenocarcinoma of the uterus

	All patients N=66	RT N=18	ChemoRT N=44	p-value
Median age (years)	59 (range, 33–77)	63	57.5	0.04 *
Median tumor size (cm)	4 (range, 2–12)	4	4.4	0.2
Grade				
1	14 (21%)	5 (28%)	8 (18%)	0.14
2	30 (45%)	10 (56%)	17 (39%)	
3	22 (33%)	3 (17%)	19 (43%)	
Lymphovascular invasion	47 (71%)	12 (67%)	33 (75%)	0.5
MMI				
None	4 (6%)	2 (11%)	1 (2%)	0.3
<50%	17 (26%)	5 (28%)	11 (25%)	
>50%	45 (68%)	11 (61%)	32 (73%)	
Cervical stromal involvement	20 (30%)	5 (18%)	13 (30%)	1.0
Positive peritoneal cytology	12 (18%)	2 (11%)	9 (20%)	0.5
Adnexal involvement	18 (28%)	1 (6%)	16 (37%)	0.01 *
Site of nodal involvement				
Pelvic	56 (85%)	17 (94%)	36 (82%)	0.4
Para-aortic	5 (8%)	0	4 (9%)	
Both pelvic and para-aortic	5 (8%)	1 (6%)	4 (9%)	
Median number of LN removed	11 (range, 1–45)	11 (range, 2–24)	11 (range, 1–45)	0.9
Pelvic	10	11	10	
PAN	3	5	3	
Median number of LN +	2 (range, 1–9)	1 (range, 1–5)	2 (range, 1–9)	0.02 *
Pelvic +	1	1	2	
PAN +	1	3	1	

Abbreviations: FIGO, International Federation of Obstetrics and Gynecology; RT, radiotherapy; chemoRT, combined chemotherapy and radiotherapy; MMI, myometrial invasion; LN, lymph nodes, PAN, para-aortic; +, positive.

* statistically significant

Table 2

Univariate analysis for DFS and OS.

	DFS		OS	
	Unadjusted HR	95% CI	Unadjusted HR	95% CI
Age	1.07/year *	1.02–1.12	1.07/year *	1.01–1.14
Tumor size	1.17/cm *	0.95–1.41	1.11/cm	0.81–1.43
Grade				
2 vs. 1	1.9 *	0.4–13.1	4.0	0.7–77
3 vs. 2	2.1 *	0.8–6.1	0.9	0.3–2.9
Lymphovascular invasion	2.7 *	0.9–11.5	2.3	0.6–15.0
MMI				
>50% vs. <50%	2.8 *	0.9–11.9	2.7	0.7–17.3
Cervical stromal involvement	3.4 *	1.4–8.6	3.2 *	1.1–10.0
Positive peritoneal cytology	0.6	0.1–1.9	0.5	0.1–2.1
Adnexal involvement	1.3	0.4–3.2	1.2	0.3–3.7
Site of nodal involvement				
PAN+ vs. pelvic+	1.6	0.5–4.1	0.6	0.1–2.4
Number of LN removed	0.97	0.90–1.03	0.97	0.90–1.04
Number of LN +	1.0	0.8–1.3	0.97	0.7–1.3
ChemoRT vs. RT alone	0.48 *	0.17–1.42	0.19 *	0.05–0.67

Abbreviations: DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; MMI, myometrial invasion; PAN, para-aortic; +, positive; LN, lymph nodes, chemoRT, combined chemotherapy and radiotherapy; RT, radiotherapy.

* covariates with $p < 0.2$ included in multivariate model

Table 3

Multivariate analysis for DFS and OS

	DFS		OS	
	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age (per year)	-	-	1.08 (1.01–1.15)	0.02
Deep MMI (> 50%)	7.5 (1.6–60)	<0.01	-	-
Tumor grade				
2 vs. 1	3.0 (0.4–60)	<0.01	-	-
3 vs. 2	6.0 (1.6–28)			
Cervical involvement	-	-	3.7 (1.04–14.3)	0.04
ChemoRT vs. RT alone	0.12 (0.03–0.49)	<0.01	0.20 (0.05–0.75)	0.02

Abbreviations: DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; MMI, myometrial invasion; chemoRT, combined chemotherapy and radiation

Table 4

Patterns of failure by use of RT and treatment fields

	Pelvis	PAN	Intra-abdominal	Distant	Total [*]
No RT	3 (75%)	2 (50%)	0	0	3/4 (75%)
Pelvic RT	2 (5%)	5 (12%)	0	3 (7%)	9/41 (22%)
Extended field RT	1 (7%)	1 (7%)	0	2 (13%)	3/15 (20%)
Whole abdominal RT	0	0	1 (17%)	2 (33%)	2/6 (33%)

Abbreviations: RT, radiotherapy; PAN, para-aortic lymph nodes

^{*} Number of patients with treatment failure divided by total number at risk