Gynecologic Oncology 152 (2019) 26–30

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Adjuvant therapy in stage III endometrial cancer confined to the pelvis

Reem Albeesh [a], Guy-Anne Turgeon [a], Joanne Alfieri [a], José João Mansure [b], Lili Fu [c], Jocelyne Arseneau [c], Xing Zeng [d], Kris Jardon [d], Lucy Gilbert [d], Luis Souhami [a,*]

[a] Department of Radiation Oncology, McGill University Health Centre, Cedars Cancer Centre, Canada
[b] Oncology Research Unit, McGill University Health Centre, Cedars Cancer Centre, Canada
[c] Department of Pathology, McGill University Health Centre, Cedars Cancer Centre, Canada
[d] Department of Gynecological Oncology, McGill University Health Centre, Cedars Cancer Centre, Canada

HIGHLIGHTS

- Adding chemotherapy didn't improve the survival compared to radiation therapy alone.
- Grade 3 disease was an independent predictor for worse outcomes.
- Patients with grade 3 disease appear to benefit from chemotherapy.

ARTICLE INFO

Article history:
Received 15 October 2018
Accepted 3 November 2018
Available online 22 November 2018

Keywords:
Endometrial cancer
Stage 3
Radiotherapy
Chemotherapy
Adjuvant therapy

ABSTRACT

Objective. To review outcomes of patients with stage III endometrial cancer confined to the pelvis treated with adjuvant pelvic radiotherapy (RT) or sequential chemoradiotherapy (CRT).

Methods. Between 1990 and 2012, 144 patients diagnosed with stage IIIA, B or C1 endometrial cancer were treated in our institution. All were treated with total hysterectomy, bilateral salpingo-oophorectomy ± lymph node dissection. Post-operatively, 67 patients received adjuvant RT alone, 37 CRT, 21 chemotherapy alone and 19 had no adjuvant therapy. This analysis focuses on the 104 patients treated with RT or CRT.

Results. The median follow-up was 61 months. Forty-six patients (44%) were stage IIIA, 6 (6%) were stage IIIB and 52 (50%) stage IIIC1. The 5-year overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS) for patients treated by RT alone vs. CRT were, respectively, 67% vs. 61% ($p = 0.55$); 67% vs. 51% ($p = 0.35$); and 76% vs. 65% ($p = 0.21$). Grade 3 disease was an independent predictor for worse OS (HR = 6.01, $p = 0.001$), DFS (HR = 3.16, $p = 0.03$), and DSS (HR = 3.77, $p = 0.02$). In patients with grade 3 disease ($n = 49$), the 5-year OS was superior for the CRT (42% vs. 56%, $p = 0.007$).

Conclusions. In patients with stage III endometrial cancer confined to the pelvis, the addition of adjuvant chemotherapy with RT significantly improved OS in grade 3 disease. Grade 3 histology is a strong predictor for poor outcome. Further randomized studies aiming specifically at stage III disease are warranted.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries and its incidence is increasing, particularly in the USA, Western Europe and Canada [1]. This increase can partially be explained by the aging population, but the prevalence of obesity and metabolic syndrome in these regions certainly contributes [2]. The majority of endometrial cancer patients present with early stage disease and good prognosis. However, about 16% of patients are initially diagnosed with more advanced disease [3]. International Federation of Gynecology and Obstetrics (FIGO) stage III disease accounts for 7% of all endometrial cancer [3] and its 5-year overall survival (OS) is 57–85% [4–9]. In patients with high risk stage I–III disease, the recently reported PORTEC-3 trial demonstrated no overall survival (OS) benefit from the addition of chemotherapy to the radiotherapy [4]. In a subgroup analysis of stage III disease only (confined or not to the pelvis), the study showed a significant failure-free survival advantage for the combined approach, but at the expense of significant toxicity.

The optimal management of stage III endometrial cancer confined to the pelvis remains controversial. The purpose of this study was to review our institutional experience in the post-operative treatment of patients with stage III endometrial cancer confined to the pelvis with either adjuvant pelvic radiotherapy (RT) alone or sequential chemoradiotherapy (CRT).

* Corresponding author at: McGill University Health Centre, Cedars Cancer Centre, 1001 Decarie Boulevard, DS1-1620, Montreal, Quebec H4A 3J1, Canada.
E-mail address: luis.souhami@mcgill.ca (L. Souhami).

https://doi.org/10.1016/j.ygyno.2018.11.002
0090-8258/

2. Materials and methods

2.1. Patients

After obtaining authorization from the institutional Research Ethics Board, we retrospectively identified patients treated for endometrial cancer at our institution between 1990 and 2012, diagnosed with FIGO stage IIIA, B or C1. Re-staging was done retrospectively in patients treated prior 2009, peritoneal cytology was disregarded and patients with para-aortic lymph node (LN) involvement (stage IIIC2) were excluded. All eligible patients were diagnosed and treated with either open or laparoscopic total hysterectomy, bilateral salpingo-oophorectomy with or without pelvic/para-aortic lymph node dissection. Surgical resection was either followed by adjuvant RT alone, CRT, chemotherapy alone, or no further adjuvant treatment.

2.2. Chemotherapy

The chemotherapy regimen used in our institution during the studied period was platinum-based chemotherapy, mainly with carboplatin (AUC = 6) and paclitaxel (175 mg/m^2 IV) planned for four to six cycles and given every 3 weeks (Table 1). The number of cycles was determined based on patient tolerance. Patients treated with CRT received their chemotherapy prior to the irradiation.

2.3. Radiotherapy

External beam radiotherapy (EBRT) was delivered 5 days a week with either three-dimensional planning, using 4-field box arrangement with 18 MV photons, or intensity modulated radiotherapy (IMRT) using 6 MV photons. From July 2009, IMRT became the institution preferred delivery method. A vaginal internal target volume using a fused image of a full and empty bladder scans to account for organ motion was used for IMRT planning. A total dose of 45 Gy in 1.8 Gy per fraction was delivered to the lower common iliac nodes, the internal and external iliac nodes, the parametria, the upper vagina/para-vaginal tissue and the presacral lymph nodes (if the cervix was involved). All constraints to the organs at risks were based on standard guidelines [10,11].

Patients treated with CRT started their radiotherapy 4–6 weeks after their last chemotherapy cycle. The same dose and treatment volumes were used for both groups of patients. As it was common practice at our institution prior 2013, most patients received an intra-cavitary cervical high dose rate (HDR) brachytherapy boost dose of 6 Gy in 1 fraction or 12 Gy in 2 fractions at the end of their EBRT. Three patients in each group received brachytherapy alone to a dose of 21 Gy delivered in 3 separate fractions.

Table 1
Patients and treatment characteristics.

Characteristics	Radiation alone (n = 67)		Chemoradiation (n = 37)		p-Value
	N	%	N	%	
Median follow-up	64 months		59 months		
Age					0.84
≤65	33	49%	19	51%	
>65	34	51%	18	49%	
Pathology					0.01
Endometrioid	50	76%	18	46%	
Mixed	10	15%	8	24%	
Serous/clear cell	7	9%	11	30%	
Grade					0.006
1	19	28%	2	5%	
2	23	34%	11	30%	
3	25	37%	24	65%	
FIGO stage					0.0001
3A	41	61%	5	14%	
3B	3	5%	3	8%	
3C1	23	34%	29	78%	
Chemotherapy					
Seq carbo-taxol	–	–	26	70%	
Seq carbo-taxol & conco CDDP	–	–	3	8%	
Other platinum-based	–	–	8	22%	
Radiotherapy					
EBRT alone	19	28%	9	24%	
Brachytherapy alone	3	5%	3	8%	
EBRT + brachytherapy boost	45	67%	25	68%	
Radiotherapy technique					
3DCRT	54	84%	19	56%	
IMRT	10	16%	15	44%	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; seq = sequential; carbo-taxol = carboplatin and paclitaxel; conco = concomitant; CDDP = cisplatin; EBRT = external beam radiation therapy. Radiotherapy technique and EBRT + brachytherapy boost percentages calculated on patients receiving EBRT.

2.4. Treatment evaluation

Toxicity reporting was based on Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [12]. Acute and subacute toxicities were defined up to 6 months of completing the adjuvant treatment. During pelvic RT, patients were clinically evaluated once weekly. After treatment completion, each patient was followed with clinical examination every 3 months for the first 2 years, every 6 months for the following 3 years and yearly thereafter. Follow-up imaging and laboratorial studies were performed at the discretion of the treating physician or if clinically indicated.

2.5. Statistical analysis

Summary statistics were used to describe the population in terms of demographics, tumor and treatment characteristics. Survival was measured from the date of diagnosis to the date of death from any cause. Patients alive at the date of last contact had their survival censored at that date. The Kaplan-Meier actuarial method was used to calculate survival curves for the overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS) for both RT alone and CRT [13]. Cox proportional hazard models were used to estimate the hazard ratios (HR) of each clinico-pathologic parameter and to compare the two treatments (RT alone vs. CRT). The Chi-square test and unpaired *t*-test were used to assess the statistical significance of the difference between groups. Log-rank tests were also used to evaluate differences in the survival curves. We assessed age, disease stage, histopathology, histology grade and treatment modality in the univariable analysis to determine their potential impact on disease outcomes and a multivariable analysis was done with the significant variables. A p-value ≤ 0.05 was considered statistically significant. We performed all analysis using the Strata 13 (Strata Corporation, College Station, TX) software package.

3. Results

3.1. Demographic data

Between 1990 and 2012, 144 patients diagnosed with endometrial carcinoma FIGO stage IIIA, B or C1 were identified. Twenty-one patients received adjuvant chemotherapy alone and 19 patients received no adjuvant treatment. Those two groups were excluded from the analysis due to the relatively small number of patients. The remaining 104 patients were analyzed of which 67 patients (64%) received adjuvant RT alone and 37 patients (36%) received CRT.

Baseline characteristics of the patients are summarized in Table 1. The median follow-up for the RT and the CRT arms were, respectively, 64 months (range: 6–192) and 59 months (range: 13–146) while the median age at diagnosis was, respectively, 68 years (range: 42–89) and 64 years (range: 31–83). Patients treated with CRT had significantly more serous or clear cell histology, higher grade disease and advanced stage than patients treated with RT alone.

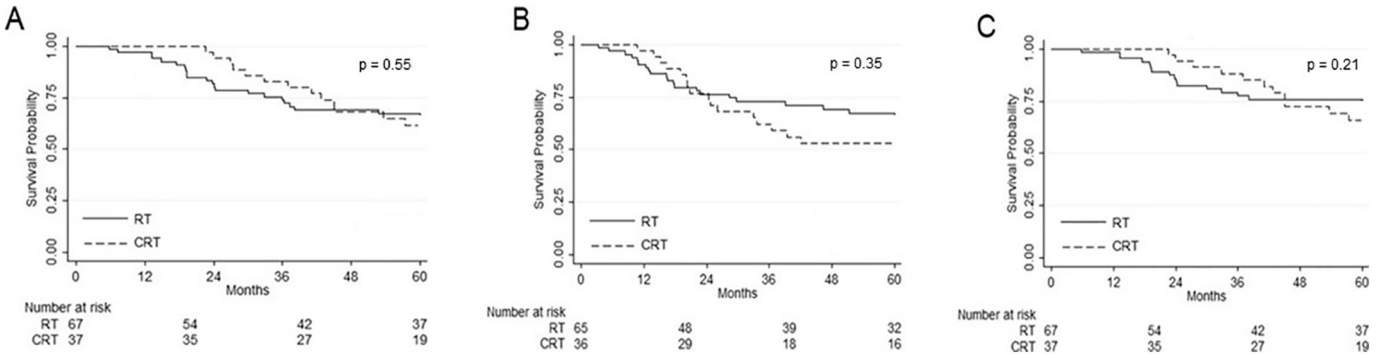

Fig. 1. Overall survival (A), disease-free survival (B) and disease-specific survival (C) for all patients.

3.2. Survival outcomes

At the time of the analysis, 33 patients (49%) in the RT arm and 16 (43%) in the CRT arm had died. The 5-year OS of RT alone was 67% (95% CI: 54–77) and 61% (95% CI: 42–75) for CRT, (Fig. 1A). This difference was not significant (p = 0.546). The 5-year DFS and DSS rates (Fig. 1B, C) for patients treated by RT alone vs. CRT were 67% (95% CI: 54–78) vs. 51% (95% CI: 33–67) and 76% (95% CI: 63 85) vs. 65% (95% CI: 46–79), respectively. These differences also did not reach statistical significance.

On uni- and multivariable analysis, grade 3 histology was the only significant variable for poor OS, DFS and DSS (Table 2). An exploratory analysis was performed on the subgroup of 49 patients with grade 3 disease, of which 25 received RT alone and 24 patients were treated with CRT. Both groups were balanced for age, but the CRT group had more patients with stage 3C1 (18 vs. 11) and serous/clear cell histology (11 vs. 7) compared to the RT alone group. The 5-year OS rates (Fig. 2A) for RT alone vs. CRT were 42% (95% CI: 23–61) and 56% (95% CI: 34–74), respectively. This difference was significant (p = 0.007). The 5-year DFS and DSS rates (Fig. 2B–C) for RT alone or CRT were 43% (95% CI: 22–63) vs. 51% (95% CI: 35–68), p = 0.27, and 59% (95% CI: 36–76) for both treatments, respectively (p = 0.20). The median OS and DFS for the RT alone vs. CRT groups were 36 vs. 77 months and 39 vs. 42 months, respectively. The RT group median DSS was 69 months and this value was unreached in the CRT patients.

3.3. Loco-regional and distant control

Table 3 shows the 5-year unadjusted pattern of failure for the 101 assessable patients and for those with grade 3 histology. There was no significant difference in patterns of failure between the two groups. Compared to patients treated with RT alone, patients treated with CRT

Table 2
Univariable and multivariable analyses for all patients.

Univariate analysis						
Variables	Overall survival		Disease-free survival		Disease-specific survival	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age						
≤65	1.00 REF		1.00 REF		1.00 REF	
>65	1.54 (0.86–2.78)	0.15	1.27 (0.68–2.41)	0.45	1.69 (0.84–3.39)	0.14
Pathology						
Endometrioid	1.00 REF		1.00 REF		1.00 REF	
Mixed	1.02 (0.48–2.17)	0.95	0.79 (0.30–2.08)	0.64	0.99 (0.40–2.48)	0.99
Serous/clear cell	1.51 (0.73–3.10)	0.26	1.67 (0.80–3.50)	0.17	1.75 (0.77–3.97)	0.18
Grade						
1	1.00 REF		1.00 (REF)		1.00 REF	
2	2.15 (0.69–6.68)	0.18	1.44 (0.49–4.22)	0.50	1.24 (0.36–4.24)	0.73
3	4.65 (1.64–13.1)	0.004	3.01 (1.15–7.90)	0.02	3.27 (1.13–9.49)	0.03
FIGO stage						
3A	1.00 REF		1.00 REF		1.00 REF	
3B	1.00 (0.29–3.35)	0.99	1.30 (0.37–4.50)	0.68	0.98 (0.22–4.36)	0.98
3C1	0.93 (0.52–1.67)	0.82	1.41 (0.73–2.74)	0.30	1.13 (0.56–2.27)	0.73
Treatment						
Radiation	1.00 REF		1.00 (REF)		1.00 REF	
Combination	0.86 (0.47–1.60)	0.64	1.33 (0.70–2.52)	0.38	1.13 (0.57–2.27)	0.72
Multivariate analysis						
Variables	Overall survival		Disease-free survival		Disease-specific survival	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Grade						
1	1.00 REF		1.00 REF		1.00 REF	
2	2.32 (0.75–7.23)	0.14	1.47 (0.49–4.31)	0.49	1.30 (0.38–4.46)	0.68
3	6.01 (2.07–17.4)	0.001	3.16 (1.14–8.74)	0.03	3.77 (1.25–11.4)	0.02
Treatment						
Radiation	1.00 REF		1.00 REF		1.00 REF	
Chemoradiation	0.53 (0.28–1.00)	0.05	0.90 (0.45–1.79)	0.77	0.73 (0.35–1.51)	0.39

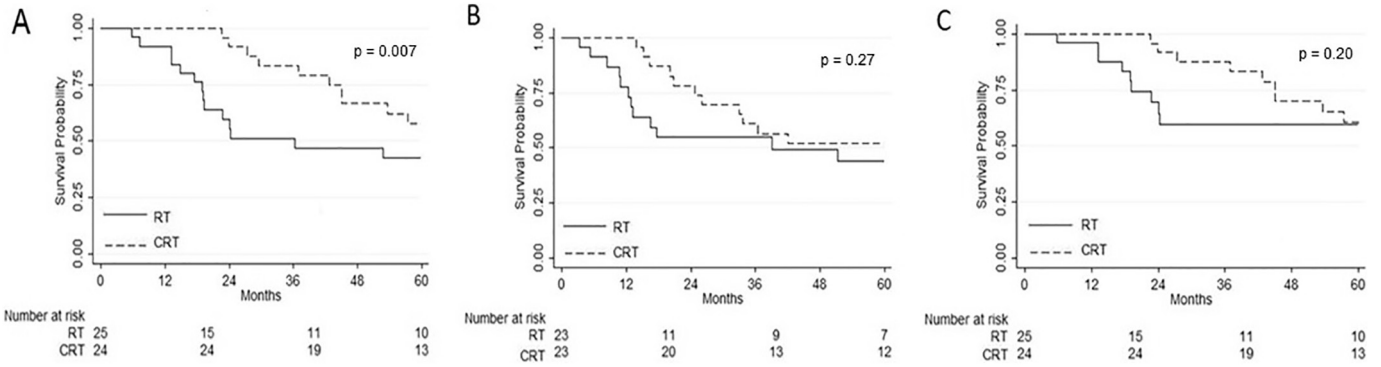

Fig. 2. Overall survival (A), disease-free survival (B) and disease-specific survival (C) for patients with grade 3 disease.

had a HR = 0.81 (95% CI, 0.32–2.10, p = 0.67) for loco-regional control and a HR = 0.87 (95% CI, 0.41–1.89, p = 0.73) for distant disease control. There was no significant difference is patterns of failure when only grade 3 histology was analyzed.

3.4. Treatment-related toxicities

All patients completed their planned radiotherapy except for one in the RT alone group due to metastatic progression on treatment. In the CRT group, 8 (22%) patients did not complete their planned chemotherapy due to the following reasons: poor tolerance (nausea, vomiting, weight loss; n = 3), small bowel obstruction (n = 1), thrombocytopenia (n = 1), ureteral stricture complicated by an iatrogenic fistula (n = 1), upper gastrointestinal bleeding (n = 1), and 1 patient developed numerous complications (febrile neutropenia, electrolyte imbalance and deep vein thrombosis).

Acute and late grade 3–4 toxicities are shown in Table 4. Acute grade 3–4 toxicities were diagnosed in 6% and 35% of patients treated with RT alone and CRT, respectively. The two with grade 4 acute toxicity were hematologic. At the time of the analysis, late grade 3 toxicity developed in 2 patients in each group. One late grade 4 toxicity occurred in a patient treated with RT alone whom developed a rectovaginal fistula necessitating a colostomy 1.5 year after treatment.

4. Discussion

The optimal post-operative adjuvant therapy for patients with stage 3 endometrial cancer confined to the pelvis remains undefined. There have been variable patterns of practice and either monotherapy or combined adjuvant therapy have been commonly used in the management of this disease stage [5]. While meta-analyses and systematic reviews [7,14] suggest a potential OS benefit for the combined approach, this has not been consistently confirmed in randomized trials [4,6]. The recently published PORTEC-3 study randomized 686 women to post-operative adjuvant RT alone versus CRT [4] and reported a lack of improvement in 5-year OS for the combination, although there was an improved failure-free survival.

One major issue with these trials is related to the heterogeneity of the population studied. Varying stages and different histologies are grouped together making the interpretation of outcomes difficult. Our aim was to explore the potential benefit of combined therapy in patients with stage 3 disease but limited to the pelvic region. Our retrospective review compares two adjuvant treatments for stage IIIA, B or C1 endometrial cancer confined to the pelvis based on the 2009 FIGO staging classification. Overall, our analysis did not show an improved OS, DFS or DSS for patients receiving CRT compared to RT alone. Similarly, there was no difference in the pattern of failures. These results are to be interpreted with caution considering the retrospective nature of the study and the imbalance in prognostic factors between the groups.

Even though level 1 evidence is lacking to support the routine use of combined adjuvant treatment in patients with stage 3 disease, its utilization has increased significantly. Boothe et al. [5] analyzed patterns of care and their impact on OS in endometrial stage III cancer diagnosed in the United States population between 2004 and 2013. A total of 21,027 patients were included in which 54% were treated with adjuvant monotherapy (chemotherapy alone or RT alone) and 46% with combined CRT. On multivariate analysis, the authors concluded that adjuvant CRT demonstrated an OS benefit compared to monotherapy (HR: 0.61, 95% CI: 0.54–0.70) and significance was maintained when CRT was compared to RT alone ($p < 0.01$) or chemotherapy alone ($p < 0.01$). When RT alone was compared with CT alone, RT alone was associated with an improved OS on multivariate analysis (HR: 0.80, 95% CI: 0.69–0.96). These findings in large patients' cohort can be significant, but those data do not seem to be reproduced in randomized controlled trial and the additive treatment toxicities are not to be neglected. The final results are pending for the GOG-258 study randomizing CRT vs. chemotherapy alone in stage III-IV disease. However, preliminary data reported as an abstract shows no differences in overall or recurrence-free survival between groups while significantly more vaginal, pelvic or para-aortic recurrence occurred in patients treated with chemotherapy alone [15].

As reported by the PORTEC 3 trial [4], our study also shows that grade 3 disease (endometrioid grade 3, serous and clear cell histology) [16] is an independent prognostic factor for outcome. The Surveillance, Epidemiology, and End Results (SEER) study reporting the outcomes of 44,000 women treated in North America, showed a 5-year survival of 60% for stage III disease [17] and among those women, the 5-year relative survival was 83%, 68%, and 48% for grade 1, 2, or 3 adenocarcinomas, respectively [17]. In a pooled data analysis of patients with advanced or

Table 3
Pattern of failure.

Treatment	5-Year loco-regional control (%)	95% CI	5-Year distant control (%)	95% CI
All patients	78	67–85	66	55–74
RT alone (n = 65)	79	66–88	73	60–82
CRT (n = 36)	75	56–87	53	35–68
Histology grade 3				
RT alone (n = 23)	70	44–86	49	27–68
CRT (n = 23)	68	43–83	52	30–70

RT = radiation therapy; CRT = sequential chemoradiation; CI = confidence interval.

recurrent endometrial cancer treated on four GOG randomized phase III chemotherapy trials, McMeekin et al. [16] found that endometrioid grade 3 tumors had an estimated odds of response 1.47 times that of patients with grade 1 disease ($p = 0.09$). Our subgroup analysis of grade 3 patients showed a significant OS benefit for patients treated with CRT and a trend toward DFS improvement.

We would certainly benefit of a better understanding of the endometrial cancer biology and its molecular profile to improve the patient selection for each treatment modality [18–21]. The TransPORTEC consortium study evaluated the molecular profile of 116 patients and found that no distant metastasis occurred in the POLE-mutant ($n = 14$) and microsatellite instable ($n = 19$) groups, while it occurred in 50% of the p53-mutant ($n = 36$) and 39% of the no specific molecular profile patients. [21] Furthermore, two targetable alterations, the PI3K-AKT pathway (60%) and hormone receptor positivity (45%), were frequently found which could lead to more effective and less toxic systemic agents.

Our results should be interpreted in the context of several limitations, including the retrospective nature of data collection, the selection bias in the administration of the CRT to healthier and higher risk patients and the lack of molecular marker studies. Furthermore, it is always possible that a less detailed recording of toxicity occurred. Despite these shortcomings, we believe that the information contained in this paper may serve as a guide to practicing gynecologic oncologists. Strengths of this study include the histopathological review of all patients by a gynecopathologist, the use of FIGO 2009 staging classification and the relatively large sample size for this specific group of patients (stage 3 disease confined to the pelvis).

5. Conclusion

In patients with stage 3 endometrial cancer confined to the pelvis, the use of adjuvant CRT was not associated with significant improvement in outcomes compared to RT alone. Patient with grade 3 histology have a worse prognosis and combined therapy may have a positive impact in outcomes for this group.

Conflict of interest

Dr. Souhami reports travel support from Varian Medical Systems, other from Janssen, other from Bayer, outside the submitted work; Dr. Zeng reports grants from Astra Zeneca - BRCA testing database, outside the submitted work; Dr. Gilbert reports personal fees from Astra Zeneca, personal fees from Advaxis, personal fees from Pfizer, personal fees from Astra Zeneca, outside the submitted work.

All authors have approved the final article.

CRediT authorship contribution statement

Reem Albeesh: Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Guy-Anne Turgeon:** Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Joanne Alfieri:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **José João Mansure:** Formal analysis, Writing - review & editing. **Lili Fu:** Writing - review & editing. **Jocelyne Arseneau:** Writing - review & editing. **Xing Zeng:** Writing - review & editing. **Kris Jardon:** Writing - review & editing. **Lucy Gilbert:** Writing - review & editing. **Luis Souhami:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing.

Table 4
Acute and late adverse events grade 3–4 as per the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [12].

Adverse event	Radiation (n = 67)	Chemoradiation (n = 37)
Acute		
Hematologic	–	8 (22%)
Genitourinary	2 (3%)	0
Gastrointestinal	2 (3%)	5 (14%)
Late		
Genitourinary	1 (1%)	0
Gastrointestinal	2[a] (3%)	1 (3%)
Neurological	0	1 (3%)

[a] Single patient with late grade 4 toxicity; n = number of patients.

References

[1] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108, https://doi.org/10.3322/caac.21262.

[2] P. Morice, A. Leary, C. Creutzberg, N. Abu-Rustum, E. Darai, Endometrial cancer, Lancet 387 (2016) 1094–1108, https://doi.org/10.1016/s0140-6736(15)00130-0.

[3] S.M. Ueda, D.S. Kapp, M.K. Cheung, et al., Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths, Am. J. Obstet. Gynecol. 198 (2008) 218.e211–218.e216, https://doi.org/10.1016/j.ajog.2007.08.075.

[4] S.M. de Boer, M.E. Powell, L. Mileshkin, et al., Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial, Lancet Oncol. 19 (2018) 295–309, https://doi.org/10.1016/s1470-2045(18)30079-2.

[5] D. Boothe, A. Orton, B. Odei, et al., Chemoradiation versus chemotherapy or radiation alone in stage III endometrial cancer: patterns of care and impact on overall survival, Gynecol. Oncol. 141 (2016) 421–427, https://doi.org/10.1016/j.ygyno.2016.03.021.

[6] T. Hogberg, M. Signorelli, C.F. de Oliveira, et al., Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies, Eur. J. Cancer 46 (2010) 2422–2431, https://doi.org/10.1016/j.ejca.2010.06.002.

[7] L. Yi, H. Zhang, J. Zou, P. Luo, J. Zhang, Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: a systematic review and meta-analysis, Gynecol. Oncol. (2018)https://doi.org/10.1016/j.ygyno.2018.03.004.

[8] D.R. Scribner Jr., L.E. Puls, M.A. Gold, A phase II evaluation of docetaxel and carboplatin followed by tumor volume directed pelvic plus or minus paraaortic irradiation for stage III endometrial cancer, Gynecol. Oncol. 125 (2012) 388–393, https://doi.org/10.1016/j.ygyno.2012.02.003.

[9] S.A. Milgrom, M.A. Kollmeier, N.R. Abu-Rustum, et al., Postoperative external beam radiation therapy and concurrent cisplatin followed by carboplatin/paclitaxel for stage III (FIGO 2009) endometrial cancer, Gynecol. Oncol. 130 (2013) 436–440, https://doi.org/10.1016/j.ygyno.2013.06.024.

[10] B. Emami, J. Lyman, A. Brown, et al., Tolerance of normal tissue to therapeutic irradiation, Int. J. Radiat. Oncol. Biol. Phys. 21 (1991) 109–122, https://doi.org/10.1016/0360-3016(91)90171-Y.

[11] L.B. Marks, E.D. Yorke, A. Jackson, et al., Use of normal tissue complication probability models in the clinic, Int. J. Radiat. Oncol. Biol. Phys. 76 (2010) S10–S19, https://doi.org/10.1016/j.ijrobp.2009.07.1754.

[12] Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE 4.0). Accessed on September 6th 2016.

[13] E.L. Kaplan, P. Meier, Nonparametric estimation from incomplete observations, J. Am. Stat. Assoc. 53 (1958) 457–481, https://doi.org/10.1080/01621459.1958.10501452.

[14] K. Galaal, M. Al Moundhri, A. Bryant, A.D. Lopes, T.A. Lawrie, Adjuvant chemotherapy for advanced endometrial cancer, Cochrane Database Syst. Rev. (2014), Cd010681. https://doi.org/10.1002/14651858.CD010681.pub2.

[15] D. Matei, V.L. Filiaci, M. Randall, et al., A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma, J. Clin. Oncol. 35 (2017) 5505, https://doi.org/10.1200/JCO.2017.35.15_suppl.5505.

[16] D.S. McMeekin, V.L. Filiaci, J.T. Thigpen, H.H. Gallion, G.F. Fleming, W.H. Rodgers, The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study, Gynecol. Oncol. 106 (2007) 16–22, https://doi.org/10.1016/j.ygyno.2007.04.032.

[17] L.A.G. Ries, J.L. Young Jr., G.E. Keel, M.P. Eisner, Y.D. Lin, M.-J.D. Horner, Cancer survival among adults: US SEER program, 1988–2001, Patient and Tumor Characteristics SEER Survival Monograph Publication, 2007 , (07-6215).

[18] N. Bansal, V. Yendluri, R.M. Wenham, The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies, Cancer Control 16 (2009) 8–13, https://doi.org/10.1177/107327480901600102.

[19] A. Thoury, V. Descatoire, L. Kotelevets, et al., Evidence for different expression profiles for c-Met, EGFR, PTEN and the mTOR pathway in low and high grade endometrial carcinomas in a cohort of consecutive women. Occurrence of PIK3CA and K-Ras mutations and microsatellite instability, Histol. Histopathol. 29 (2014) 1455–1466, https://doi.org/10.14670/hh-29.1455.

[20] T. Bosse, R.A. Nout, J.N. McAlpine, et al., Molecular classification of grade 3 endometrioid endometrial cancers identifies distinct prognostic subgroups, Am. J. Surg. Pathol. 42 (2018) 561–568, https://doi.org/10.1097/pas.0000000000001020.

[21] E. Stelloo, T. Bosse, R.A. Nout, et al., Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative, Mod. Pathol. 28 (2015) 836–844, https://doi.org/10.1038/modpathol.2015.43.