Adjuvant Treatment of Early Ovarian Clear Cell Carcinoma: A Population-Based Study of Whole Abdominal Versus Pelvic Nodal Radiotherapy

Soumyajit Roy, MBBS^{1,2,3}; Paul Hoskins, MD, FRCPC^{4,5}; Anna Tinker, MD, FRCPC^{4,5}; Harinder Brar, MD^{6,7}; Gale Bowering, BS¹; and Gaurav Bahl, MBBS, DNB, FRCPC^{1,2}

ABSTRACT

Background: Adjuvant treatment in early ovarian clear cell carcinoma (OCCC) is not yet standardized. The objective of this population-based study was to compare the outcome of patients with early OCCC treated with adjuvant chemotherapy versus chemoradiotherapy (chemoRT) and evaluate the association of adjuvant radiotherapy regimens (whole abdominal radiotherapy [WART] versus pelvic nodal radiotherapy [PRT]) with outcome. **Patients and Methods:** Chart review was conducted to identify patients with stage I and II OCCC with complete information on staging. Patients with stage IA, IB, or IC OCCC purely resulting from capsular rupture were excluded because the provincial protocol does not recommend adjuvant treatment. **Results:** Overall, 403 patients were identified and 343 received adjuvant treatment, of whom 255 had stage IC or II OCCC and 153 were eligible for final analysis. On Cox multivariable regression, receipt of chemoRT (n=90) was associated with an improvement in failure-free survival (FFS) (hazard ratio [HR], 0.57; 95% CI, 0.34–0.94) compared with chemotherapy alone (n=63). Use of chemoRT also resulted in 54% reduction in the cumulative incidence of cancer-specific mortality (subdistribution HR, 0.46; 95% CI, 0.24–0.89). However, there was no significant difference in the HR for overall survival (OS) between the chemoRT (HR, 0.70; 95% CI, 0.43–1.13) and chemotherapy group. Relative to chemotherapy + WART (chemo-WART), chemotherapy + PRT (chemo-PRT) was not associated with any significant difference in HR for FFS (HR, 1.34; 95% CI, 0.40–4.44) or OS (HR, 1.13; 95% CI, 0.37–3.46). **Conclusions:** Adjuvant chemoRT was associated with a lower risk of failure compared with chemotherapy alone. However, there was no difference in OS between the adjuvant chemotherapy and chemoRT regimens. Additionally, no significant difference in terms of FFS or OS was found between the chemo-WART and chemo-PRT groups.

J Natl Compr Canc Netw 2021;19(2):172–180
doi: 10.6004/jnccn.2020.7609

¹BC Cancer Agency, Abbotsford, British Columbia, Canada; ²Department of Surgery, University of British Columbia, Vancouver, British Columbia, Canada; ³Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and ⁴BC Cancer Agency, ⁵Department of Medicine, University of British Columbia, ⁶Vancouver General Hospital, and ⁷Department of Obstetrics & Gynecology, University of British Columbia, Vancouver, British Columbia, Canada.

Background

Ovarian clear cell carcinoma (OCCC) is a rare subtype of epithelial ovarian malignancy (EOM), accounting for approximately 5% to 10% of all EOMs in North America.^{1–3} Advanced OCCC portends poor prognosis, which is often attributed to its inherent resistance to platinum-based chemotherapy.^{4–6} In contrast, stage IA, IB, or IC disease solely caused by capsular rupture has been found to confer excellent prognosis, and therefore the benefit of adjuvant therapy is questionable.^{1,6–9} Although debulking surgery followed by platinum-based chemotherapy is the most commonly used treatment for early OCCC, controversy remains regarding optimal number of chemotherapy cycles, most effective chemotherapy regimen, and role of radiotherapy (RT) in this patient population.^{10–12}

RT has been explored as a salvage or adjuvant treatment option in OCCC. Retrospective studies have shown durable local control rates with salvage limited-field RT after first-line chemotherapy.^{11,13} A population-based study demonstrated superior disease-free survival with addition of whole abdominal RT (WART) to 3 cycles of adjuvant chemotherapy in patients with stage II OCCC or a select subgroup of patients with stage IC disease (ICo) characterized by either surface or cytologic positivity.⁸ Nagai et al¹⁴ demonstrated a survival advantage with adjuvant WART in 16 patients with stage IC–III OCCC compared with 12 patients from a historical cohort who received adjuvant platinum-based chemotherapy. Conversely, another retrospective study, combining data from 2 institutions, did not report any benefit with adjuvant WART in early OCCC.¹⁵

Although most of these studies used WART, significant concern remains regarding its practice,^{8,14,16} largely due to the technical challenges associated with its

See JNCCN.org for supplemental online content.

delivery and the substantial risk of RT-related toxicities, including bowel toxicities and secondary malignant neoplasms.^{17–19} Moreover, retrospective studies have shown that most patients with early OCCC experience a recurrence in the pelvis after surgery and adjuvant chemotherapy.^{1,13} As a result, there has been a gradual transition toward the use of pelvic nodal RT (PRT) instead of WART for these patients. Overall, the role of adjuvant RT and the preferred RT regimen for early OCCC are poorly defined. We reviewed our population database to compare the long-term outcome of patients with early OCCC treated with adjuvant chemotherapy alone versus those treated with chemoRT combination. Additionally, we evaluated and compared the oncologic outcome in patients treated with 2 adjuvant chemoRT regimens: chemotherapy + WART (chemo-WART) and chemotherapy + PRT (chemo-PRT).

Patients and Methods

In this Institutional Research Ethics Committee–approved study, retrospective chart review was conducted to collect and verify information for all patients diagnosed with stage I and II pure OCCC (using 1988 FIGO staging criteria) in all 6 provincial cancer centers of a Canadian province between January 1, 1984, and December 31, 2015. The provincial cancer registry and ovarian cancer outcome unit were used to identify patients. These centers follow the guidelines set by the provincial authority overseeing the delivery of cancer care in a province of 4.9 million people. Treatment policies are reviewed and issued by disease-specific tumor groups and are integrated into the provincially disseminated management protocols. These guidelines and protocols are available on the provincial cancer agency website. Policy and protocols are reviewed regularly as new data become available.²⁰ The standard, uniformly applied surgery consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, washings, and removal of suspicious nodes. Routine pelvic and/or para-aortic lymphadenectomy was not mandated. The provincial protocol did not recommend adjuvant treatment in stage IA or IB, or IC OCCC purely resulting from capsular rupture, and therefore these patients were excluded from the final analysis; only patients with stage ICo (characterized by either surface and/or cytologic positivity) or II disease were included for final analysis (see supplemental eFigure 1, available with this article at JNCCN.org). Patients were categorized into 2 groups based on cytologic finding: those with stage IC OCCC and positive peritoneal washing and/or positive ascitic cytology and those with stage IIC constituted group 1 (cytology positive), and others were categorized as group 2 (cytology negative).

Since 2000, standard provincial treatment in chemo-WART group consisted of 3 cycles of carboplatin (area

under the curve [AUC], 5–6) and paclitaxel (175 mg/m²) every 3 to 4 weeks followed by abdominopelvic irradiation. RT was initiated 3 to 4 weeks after the third cycle of chemotherapy. Pelvic RT was administered to a midplane dose of 22.5 Gy in 10 fractions over 2 weeks. This was followed by WART to a midplane dose of 22.5 Gy in 22 fractions over 4.5 weeks. Prior to 2000, the chemo-WART protocol included chemotherapy with 3 cycles of cisplatin (75 mg/m²) and cyclophosphamide (600 mg/m²) every 4 weeks followed by abdominopelvic RT (same time/dose/fraction regimen) followed by another 3 cycles of the same chemotherapy. Since 2012, RT transitioned to PRT as a provincial policy. Before 2012, pelvic RT was offered at physician's discretion. The protocol for the chemo-PRT group called for 3 cycles of carboplatin and paclitaxel (same dosage) every 3 to 4 weeks followed by external-beam RT to the pelvis to a total dose of 45 Gy in 25 fractions over 5 weeks. Standard treatment of patients in the chemotherapy group included 6 cycles of paclitaxel (175 mg/m²) and carboplatin (AUC, 5–6) combination every 3 to 4 weeks (since 2000) or 6 cycles of cisplatin (75 mg/m²) and cyclophosphamide (600 mg/m²) every 4 weeks prior to 2000.⁸ Further details of RT and posttreatment follow-up policy are summarized in supplemental eAppendix 1.

Statistics

The objectives of this study were to determine the adjusted treatment effects of adjuvant treatment (chemotherapy vs chemoRT) and RT regimen (chemo-WART vs chemo-PRT) on failure-free survival (FFS) and overall survival (OS) after adjustment for covariables. FFS was defined as time from surgery to the first of either disease failure, disease progression, or death caused by cancer. For FFS, patients who were event-free at the time of analysis were censored at their date of last follow-up with known disease status. For OS, patients were censored at the date they were last known to be alive. Median follow-up was estimated using reverse Kaplan-Meier method. Cox multivariable regression models were applied to estimate adjusted treatment effects (cause-specific hazard ratio [CSHR] with 95% CI). Stage, risk group, year of diagnosis, and age at diagnosis were included as covariables in the regression models. Patients were stratified into 3 groups (1984–1994, 1995–2004, and 2005–2014) based on year of diagnosis. Efron's method was used for handling ties.²¹ Proportionality assumptions were tested.²² Sensitivity analyses were performed by applying inverse probability weighting (IPW)–adjusted Kaplan-Meier methods to estimate survival for the chemo-WART and chemo-PRT groups after adjustment for age at diagnosis, risk group, year of diagnosis, and stage at diagnosis as covariables. IPW-adjusted log-rank tests and Cox multivariable regressions were applied to

Table 1. Patient Characteristics

Characteristic	Chemotherapy n (%)	Chemo-WART n (%)	Chemo-PRT n (%)	P Value ^a
Total, n	63	48	42	
Median age at diagnosis (IQR), y	58.1 (48.3–64.3)	57 (50.3–64.0)	55.1 (49.4–61.9)	.95
Ethnicity				.88
Asian	10 (15.9)	7 (14.6)	7 (16.7)	
Non-Asian	53 (84.1)	41 (85.4)	35 (83.3)	
Cancer stage (FIGO 1988)				.49
IC	37 (58.7)	34 (70.8)	27 (64.3)	
IIA	2 (3.2)	2 (4.2)	1 (2.3)	
IIB	2 (3.2)	4 (8.3)	2 (4.8)	
IIC	22 (34.9)	8 (16.7)	12 (28.6)	
Risk group				.63 ^b
Group 1/cytology positive	44 (70)	31 (64.6)	31 (73.8)	
Stage IC positive cytology alone	11 (17.5)	6 (12.5)	2 (4.8)	
Stage IC positive cytology + surface deposit	2 (3.2)	1 (2.1)	3 (7.0)	
Stage IC positive cytology + capsule rupture	6 (9.6)	14 (29.1)	12 (28.6)	
Stage IC positive cytology + surface deposit + capsule rupture	3 (4.8)	2 (4.2)	2 (4.8)	
Stage IIC	22 (34.9)	8 (16.7)	12 (28.6)	
Group 2/cytology negative	19 (30)	17 (35.4)	11 (26.2)	
Year of diagnosis				.001
1984–1994	18 (28.6)	25 (52.1)	0 (0)	
1995–2004	25 (39.7)	17 (35.4)	2 (4.8)	
2005–2015	20 (31.7)	6 (12.5)	40 (95.2)	

Abbreviations: chemo, chemotherapy; IQR, interquartile range; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

^aBold indicates statistically significant *P* value.

^b*P* value from comparison of group 1 and group 2.

compare the HR for FFS and OS between the 2 chemoRT regimens.^{23–25} Additionally, flexible parametric models for time-to-event data were applied to calculate the treatment effect on FFS and OS adjusted for covariables and time (supplemental eAppendix 2 and eTables 2–5).²⁶

The competing risk models of Fine and Gray²⁷ were applied to determine the cumulative incidence of treatment failure and cancer-specific mortality (CSM) among the treatment groups. Adjusted subdistribution HRs (SHR) were estimated using competing risk regression models. Non-cancer-related deaths (ie, not due to disease failure or treatment-related toxicities) were considered competing events for CSM. Deaths from any cause were considered competing events for failure. Statistical analyses were performed using R statistical version 3.5.2 (R Foundation for Statistical Computing).^{22–28}

Results

A total of 403 patients with early OCCC were identified who had complete information for staging and risk stratification. Of them, 343 received adjuvant treatment

with chemotherapy or chemoRT and 153 were eligible for final analysis. Overall, 41% (n=63) of eligible patients received adjuvant chemotherapy, whereas 59% (n=90) received adjuvant chemoRT, of whom 48 received WART and 42 received PRT (supplemental eFigures 2 and 3). Median age of the evaluable study population was 55.5 years (interquartile range [IQR], 48.4–66.6 years). Median ages of the chemotherapy, chemo-WART, and chemo-PRT groups were 58.1 (IQR, 48.3–64.3), 57 (IQR, 50.3–64.0), and 55.1 (IQR, 49.4–61.9) years, respectively. Table 1 summarizes the distribution of stage, year of diagnosis, and risk category in the treatment groups.

Some deviation from protocol-defined treatment was noted in the treatment groups (supplemental eTable 1). In the chemo-PRT group, 3D conformal RT (3D-CRT) with 4-field beam arrangement was used in 34 patients, and intensity-modulated RT (IMRT) and volumetric modulated arc therapy (VMAT) were used in 4 and 3 patients, respectively. One patient received RT using parallel opposed (anterior and posterior) radiation

portals. There was no significant difference ($P=.87$) in the proportion of patients who underwent pelvic or para-aortic lymphadenectomy among the 3 treatment groups. Median follow-up for the entire cohort was 9.1 years, whereas median follow-up for the chemo-WART, chemotherapy, and chemo-PRT groups was 16.2 (IQR, 10.1–24.2), 8.0 (IQR, 5.4–16.5), and 4.8 years (IQR, 2.7–5.7 years), respectively. At last-follow-up, 8 and 18 patients were alive without evidence of disease in the chemotherapy and chemoRT groups, respectively.

FFS at 5 years was 57.2% and 45.9% for the adjuvant chemoRT and chemotherapy groups, respectively (Figure 1A). Receipt of chemoRT was associated with a significant improvement in FFS (CSHR, 0.57; 95% CI, 0.34–0.94; $P=.03$) compared with chemotherapy alone (Table 2).

Five-year FFS was 60.6% and 53.8% for chemo-WART and chemo-PRT groups, respectively (Figure 1B). No significant difference was noted in the HR for FFS between the chemo-WART and chemo-PRT groups (CSHR, 1.34; 95% CI, 0.40–4.44, $P=.63$). Patterns of failure in the treatment groups are summarized in Table 3. There was a significant difference between the 2 RT groups with respect to overall nodal failure ($P=.007$), with higher nodal failure rates observed in the chemo-PRT group; however, no difference was seen with respect to overall peritoneal ($P=.76$) or local failure ($P=.45$), respectively. Based on IPW-adjusted Kaplan-Meier method, 5-year FFS for the chemo-WART and chemo-PRT groups was 43.9% and 34.8%, respectively. No significant difference in FFS was

found between the 2 RT regimens on IPW-adjusted log-rank test ($P=.21$) and multivariable regression (HR, 1.64; 95% CI, 0.67–3.99).

Cumulative incidence of failure at 5 years was 53.4% versus 41.1% for the adjuvant chemotherapy and chemoRT groups, respectively (supplemental eFigure 4). Receipt of adjuvant chemoRT was associated with reduced risk of cumulative incidence of failure (SHR, 0.51; 95% CI, 0.28–0.90; $P=.02$). However, no significant difference was found in the relative incidence of failure between chemo-WART and chemo-PRT groups (SHR, 1.32; 95% CI, 0.34–5.13; $P=.69$) (Table 4).

OS at 5 and 10 years was 65.8% and 54.1% for the chemoRT group and 65% and 39.2% for chemotherapy group, respectively (Figure 2A). We found no significant difference in the HR for OS between the chemotherapy and chemoRT groups (CSHR, 0.70; 95% CI, 0.43–1.13; $P=.14$).

For chemo-WART and chemo-PRT groups, 5-year OS was 67.4% and 67.9%, respectively (Figure 2B). No significant difference was noted in the HR for OS between the 2 groups (CSHR, 1.13; 95% CI, 0.37–3.46; $P=.83$) (Table 2). On IPW-adjusted analysis, 5-year OS was 46.3% and 43.4% for chemo-WART and chemo-PRT groups, respectively. We did not find any significant difference between the 2 groups on IPW-adjusted log-rank test ($P=.24$) or multivariable regression (HR, 1.74; 95% CI, 0.75–4.04).

Overall, 55 patients were noted to have cancer-specific deaths: 52 (94.5%) due to disease failure and

Figure 1. Kaplan-Meier curves showing FFS for (A) adjuvant chemotherapy and chemoRT groups and (B) chemo-WART and chemo-PRT groups. Abbreviations: chemo, chemotherapy; chemoRT, chemoradiotherapy; FFS, failure-free survival; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

Table 2. Cox Multivariable Regression Models for FFS and OS

Variable	OS		FFS	
	Adjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value ^a
Adjuvant Chemotherapy vs Chemoradiotherapy				
Age at diagnosis	1.01 (0.99–1.03)	.32	0.99 (0.96–1.01)	.24
Risk group				
Group 2/cytology negative	Ref		Ref	
Group 1/cytology positive	1.82 (0.96–3.43)	.07	2.65 (1.20–5.84)	.02
Treatment group				
Chemotherapy	Ref		Ref	
Chemoradiotherapy	0.70 (0.43–1.13)	.14	0.57 (0.34–0.94)	.03
Cancer stage (FIGO 1988)				
IC	Ref		Ref	
IIA/IIB	0.64 (0.21–1.93)	.42	0.82 (0.46–1.44)	.48
IIC	0.71 (0.40–1.25)	.23	0.83 (0.40–1.54)	.48
Year of diagnosis				
1984–1994	Ref		Ref	
1995–2004	0.86 (0.46–1.65)	.67	0.78 (0.63–2.06)	.68
2005–2015	1.56 (0.85–2.85)	.15	1.14 (0.96–1.01)	.24
Adjuvant Chemo-WART vs Chemo-PRT				
Age at diagnosis	1.01 (0.98–1.04)	.56	1.00 (0.96–1.04)	.96
Risk group				
Group 2/cytology negative	Ref		Ref	
Group 1/cytology positive	1.87 (0.71–4.92)	.21	4.68 (1.29–16.96)	.02
Treatment group				
Chemo-WART	Ref		Ref	
Chemo-PRT	1.13 (0.37–3.46)	.83	1.34 (0.40–4.44)	.63
Cancer stage (FIGO 1988)				
IC	Ref		Ref	
IIA/IIB	0.44 (0.10–2.15)	.31	1.20 (0.20–7.33)	.84
IIC	0.57 (0.25–1.38)	.22	0.36 (0.13–1.01)	.05
Year of diagnosis				
1984–1994	Ref		Ref	
1995–2004	2.20 (0.83–5.88)	.12	2.29 (0.77–6.79)	.14
2005–2015	2.27 (0.66–7.82)	.20	2.06 (0.55–7.65)	.28

Abbreviations: Chemo, chemotherapy; FFS, failure-free survival; HR, hazard ratio; OS, overall survival; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

^aBold indicates statistically significant *P* value.

3 (5.5%) due to treatment-related toxicities that included radiation-induced small bowel obstruction (n=1) and radiation-induced liver disease (n=1) in the chemo-WART group and thromboembolic complication (n=1) in the chemo-PRT group. Cause of death could not be ascertained in 3 patients. Receipt of chemoRT was associated with a 54% reduced risk of CSM (SHR, 0.46; 95% CI, 0.24–0.89; *P*=.02) compared with chemotherapy. However, chemo-PRT (SHR, 0.72; 95% CI, 0.18–2.80;

P=.63) was not associated with any significant difference in the risk of CSM compared with chemo-WART (Table 4).

Discussion

Our findings suggest long-term reduction in the risk of failure with receipt of adjuvant chemoRT. Compared with the previous study from our province, in which the study population included all patients with stage I and II

Table 3. Sites of Treatment Failure

Site of Failure	Number of Failures ^a			P Value ^{b,c}
	Chemotherapy	Chemo-WART	Chemo-PRT	
Total	63	48	42	
Nodal				.02
Para-aortic	4	0	6	
Pelvic	4	0	1	
Supraclavicular	1	3	1	
Peritoneal				.91
Intrapelvic localized	1	1	1	
Extrapelvic localized	3	4	1	
Diffuse peritoneal involvement/ascites	7	4	3	
Local				.001
Intrapelvic	17	4	1	
Intra-abdominal	1	1	2	
Hematogenous ^a				.94
Intrathoracic	5	4	5	
Liver	4	5	3	
Skeletal	2	0	1	
Brain	1	1	1	
Spleen	3	0	1	

Abbreviations: Chemo, chemotherapy; PRT, chemo-pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

^aSeveral patients had multisite failure (14 patients in chemotherapy group, 10 patients in chemo-WART group, and 7 in chemo-PRT group).

^bP values are from Fisher exact test (bold indicates statistically significant P value) comparing nodal failure, peritoneal failure, local failure, and hematogenous failure among the treatment groups.

^cBold indicates statistically significant P value.

OCCC with year of diagnosis restricted to 2008, we included all patients with early OCCC diagnosed in 1984 through 2015 and treated with adjuvant chemotherapy or chemoRT. The comparison of treatment was, however, restricted to patients with stage II disease and those with stage IC disease and presence of malignant cells in the ascites or peritoneal washings or tumor deposits on the surface of ovary (alone or in combination). Findings from the sensitivity analyses were consistent with the primary analyses. Improved FFS with adjuvant chemoRT could be attributed to superior local control and possible sterilization of microscopic disease in the pelvic and para-aortic lymph nodes with the addition of RT to adjuvant chemotherapy. Reduction in the risk of failure might have translated into improved CSM with receipt of chemoRT. This observation concurs with a recent retrospective study that revealed inferior survival in patients with OCCC who had disease progression after adjuvant treatment.²⁹ We found a relatively higher number of para-aortic nodal failures in the chemo-PRT group compared with the chemo-WART group despite statistically similar rates of lymphadenectomy. Whether this could be reduced with the addition of para-aortic nodal RT to standard PRT target without increasing treatment-related

morbidity should be investigated in additional studies. We did not find any statistically significant difference in OS, FFS, or CSM between the 2 RT regimens. A shorter follow-up and consequent lack of events in the chemo-PRT group in addition to the overall small patient population might have resulted in a corresponding loss of power in our study. This could be reflected in the relatively wide confidence intervals. The lack of OS difference among the groups could also be explained by the limited power.

Although the primary aim of this study was not to compare toxicities among the treatment groups, note was made of 2 deaths from treatment-related toxicities in the chemo-WART group and 1 in the chemotherapy group. This must be interpreted considering that there was no (WART group) or limited use of IMRT (PRT group) in our study. A randomized study compared 3D-CRT with IMRT in patients with locally advanced cervical cancer treated with PRT with concomitant chemotherapy. IMRT yielded reduced risk of acute and late gastrointestinal toxicities.³⁰ Another nonrandomized phase II study evaluated the safety of IMRT-based consolidative WART in stage III ovarian cancer after surgery and platinum-based chemotherapy. Despite using a relatively higher dose (30 Gy in 20 fractions), no acute or late grade ≥ 3

Table 4. Competing Risk Regression for Cumulative Incidence of CSM and Failure

Variable	CSM		Failure	
	SHR (95% CI)	P Value ^a	SHR (95% CI)	P Value ^a
Adjuvant Chemotherapy vs Chemoradiotherapy				
Age at diagnosis	0.98 (0.96–1.01)	.15	0.98 (0.96–1.01)	.15
Risk group				
Group 2/cytology negative	Ref		Ref	
Group 1/cytology positive	4.25 (1.57–11.52)	.004	2.28 (1.02–5.11)	.04
Treatment group				
Chemotherapy	Ref		Ref	
Chemoradiotherapy	0.46 (0.24–0.89)	.02	0.51 (0.28–0.90)	.02
Cancer stage (FIGO 1988)				
IC	Ref		Ref	
IIA/IIB	0.83 (0.17–4.03)	.82	0.49 (0.12–1.96)	.31
IIC	0.65 (0.32–1.32)	.23	0.91 (0.49–1.71)	.78
Year of diagnosis				
1984–1994	Ref		Ref	
1995–2004	0.43 (0.18–1.04)	.06	0.57 (0.27–1.19)	.14
2005–2015	0.73 (0.37–1.46)	.38	0.77 (0.96–1.01)	.16
Adjuvant Chemo-WART vs Chemo-PRT				
Age at diagnosis	1.03 (0.98–1.08)	.27	0.99 (0.96–1.04)	.90
Risk group				
Group 2/cytology negative	Ref		Ref	
Group 1/cytology positive	8.65 (3.88–29.73)	.001	6.23 (1.33–29.31)	.02
Treatment group				
Chemo-WART	Ref		Ref	
Chemo-PRT	0.72 (0.18–2.80)	.63	1.32 (0.34–5.13)	.69
Cancer stage (FIGO 1988)				
IC	Ref		Ref	
IIA/IIB	8.68 (0.59–12.84)	.12	1.64 (0.23–11.73)	.62
IIC	0.47 (0.15–1.47)	.19	0.52 (0.18–1.51)	.23
Year of diagnosis				
1984–1994	Ref		Ref	
1995–2004	4.31 (0.91–20.47)	.07	2.86 (0.87–9.36)	.08
2005–2015	1.80 (0.98–1.08)	.27	1.55 (0.36–6.70)	.56

Abbreviations: Chemo, chemotherapy; CSM, cancer-specific mortality; PRT, pelvic nodal radiotherapy; SHR, subdistribution hazard ratio; WART, whole abdominal radiotherapy.

^aBold indicates statistically significant *P* value.

renal, hepatic, or gastrointestinal toxicities were found.³⁰ Overall, these findings suggest that use of IMRT or VMAT could potentially allow safe delivery of a higher dose of RT. Whether such dose escalation has the potential to enhance disease control without exacerbating treatment-induced morbidities in early OCCC needs further investigation.

We acknowledge several other limitations of this retrospective study. The findings are subject to bias considering evolving standards of staging, diagnostic evaluation,

and treatment techniques in the domain of surgery, chemotherapy, and RT over the span of the study.³¹ All treatment modalities had remarkable advancements during the study period that might have implications on our observations.^{32,33} Similarly, there has been significant improvement in the accuracy and reliability of diagnostic imaging for ovarian malignancies. Our study period started in an era when there was a lack of contrast-enhanced CT scans, which are now the preferred imaging modality when there is a suspicion of recurrence. Furthermore, RT was not

Figure 2. Kaplan-Meier curves showing OS for (A) adjuvant chemotherapy and chemoRT groups and (B) chemo-WART and chemo-PRT groups.

Abbreviations: chemo, chemotherapy; chemoRT, chemoradiotherapy; OS, overall survival; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

randomly allocated in this study. Therefore, one cannot rule out the influence of unforeseen confounding variables. Despite existence of standard uniform provincial guidelines, unexplained heterogeneity among the centers and treating physicians cannot be ruled out. This is pertinent for our study because a significant proportion of patients were treated before guidelines on peer review of clinical decision, target volume delineation, and plan evaluation were endorsed and implemented in the field of RT.³⁴ Sharp dissection, a previously found predictor of failure and death, was not incorporated in the regression models. Further caution is needed in interpreting the results due to exclusion of patients who received no adjuvant treatment or those with missing information on histopathology or cytology. We performed electronic and paper chart review for all patients to update follow-up; ensure meticulous reporting of disease stage, death, and its cause; and record sites of treatment failure. Nonetheless, studies with such prolonged time span are prone to attrition bias due to loss of follow-up and migration of individual subjects in and out of the population database over time.

Previous retrospective studies have shown positive cytology to be an adverse prognostic factor.^{11,35,36} Our findings were congruent with these studies. The failure pattern in our study is also consistent with other series.^{6,7,13,14} However, our findings contrast with those of a recent study by Hogen et al,¹⁵ which did not show any advantage of adjuvant RT in patients with early OCCC. The discordance in findings could be ascribed to several factors, including differences in patient population,

surgical protocols, or adjuvant treatment paradigm. To explain further, cytology was optional as part of surgical procedure in this study, which pooled patient data from 2 institutions. The comparison between adjuvant RT and no RT groups was confounded by higher use of comprehensive surgical staging in the no-RT group. The groups were heterogeneous with respect to the proportion of patients who received chemotherapy; 70% of patients in the no-RT group received adjuvant chemotherapy, whereas 84% in the RT group were treated with a chemoRT combination.

Conclusions

This population-based study showed that combination of adjuvant chemotherapy and RT was associated with encouraging long-term improvement in risk of failure and CSM, although this combination was not associated with any significant OS benefit. Our study did not find any statistically significant difference in the hazard for OS, FFS, and CSM between adjuvant PRT and WART in conjunction with chemotherapy. A randomized study should be considered to validate the findings of the current report.

Submitted March 5, 2020; accepted for publication June 26, 2020.
Published online September 24, 2020.

Previous presentation: Part of this study was presented as an oral presentation at the 59th Annual Meeting of American Society for Radiation Oncology; September 24–27, 2017; San Diego, California (Int J Radiat Oncol Biol Phys 2017;99:S110–111).

Author contributions: Study concept and design: Roy, Bahl. Provision of study material or patients: Roy, Hoskins, Tinker, Bahl. Administrative support: Bowering. Data collection and assembly: Roy, Bowering. Data analysis and

interpretation: Roy, Hoskins, Bahl. Manuscript writing: All authors. Final approval of manuscript: All authors.

Disclosures: Dr. Bahl has disclosed that he receives honoraria from Bayer, Janssen, and Sanofi. The remaining authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

Funding: This project was supported by Radiotherapy Education Process Fund, BC Cancer Agency, Abbotsford, British Columbia, Canada.

Correspondence: Gaurav Bahl, MBBS, DNB, FRCPC, Department of Radiation Oncology, BC Cancer Agency, 32900 Marshall Road, Abbotsford, British Columbia, V2S 0C2, Canada. Email: Gaurav.bahl@bccancer.bc.ca

References

- Chan JK, Teoh D, Hu JM, et al. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. *Gynecol Oncol* 2008;109:370–376.
- Tan DSP, Kaye S. Ovarian clear cell adenocarcinoma: a continuing enigma. *J Clin Pathol* 2007;60:355–360.
- Anglesio MS, Carey MS, Köbel M, et al. Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Carcinoma Study. *Int J Gynecol Cancer* 2011;121:407–415.
- Takano M, Sugiyama T, Yaegashi N, et al. Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study. *Int J Gynecol Cancer* 2008;18:937–942.
- Pathe S, Quinn MA. Clear-cell cancer of the ovary-is it chemosensitive? *Int J Gynecol Cancer* 2005;15:432–437.
- Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. *Cancer* 2000;88:2584–2589.
- Takano M, Kikuchi Y, Yaegashi N, et al. Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging. *Br J Cancer* 2006;94:1369–1374.
- Hoskins PJ, Le N, Gilks B, et al. Low-stage ovarian clear cell carcinoma: population-based outcomes in British Columbia, Canada, with evidence for a survival benefit as a result of irradiation. *J Clin Oncol* 2012;30:1656–1662.
- Chan JK, Tian C, Fleming GF, et al. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. *Gynecol Oncol* 2010;116:301–306.
- del Carmen MG, Birrer M, Schorge JO. Clear cell carcinoma of the ovary: a review of the literature. *Gynecol Oncol* 2012;126:481–490.
- Shu CA, Zhou Q, Jotwani AR, et al. Ovarian clear cell carcinoma, outcomes by stage: the MSK experience. *Gynecol Oncol* 2015;139:236–241.
- Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. NCCN Guidelines Insights: Ovarian Cancer, Version 1.2019. *J Natl Compr Canc Netw* 2019;17:896–909.
- Macrie BD, Strauss JB, Helenowski IB, et al. Patterns of recurrence and role of pelvic radiotherapy in ovarian clear cell adenocarcinoma. *Int J Gynecol Cancer* 2014;24:1597–1602.
- Nagai Y, Inamine M, Hirakawa M, et al. Postoperative whole abdominal radiotherapy in clear cell adenocarcinoma of the ovary. *Gynecol Oncol* 2007;107:469–473.
- Hogen L, Thomas G, Bernardini M, et al. The effect of adjuvant radiation on survival in early stage clear cell ovarian carcinoma. *Gynecol Oncol* 2016;143:258–263.
- Swenerton KD, Santos JL, Gilks CB, et al. Histotype predicts the curative potential of radiotherapy: the example of ovarian cancers. *Ann Oncol* 2011;22:341–347.
- Engelen MJA, Snel BJ, Schaapveld M, et al. Long-term morbidity of adjuvant whole abdominal radiotherapy (WART) or chemotherapy for early stage ovarian cancer. *Eur J Cancer* 2009;45:1193–1200.
- Whelan TJ, Dembo AJ, Bush RS, et al. Complications of whole abdominal and pelvic radiotherapy following chemotherapy for advanced ovarian cancer. *Int J Radiat Oncol Biol Phys* 1992;22:853–858.
- Einhorn N, Tropé C, Ridderheim M, et al. A systematic overview of radiation therapy effects in ovarian cancer. *Acta Oncol* 2003;42:562–566.
- Cancer Management Guidelines. Accessed May 11, 2020. Available at: <http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-guidelines>
- Efron B. The efficiency of Cox's likelihood function for censored data. *J Am Stat Assoc* 1977;72:557–565.
- Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. Accessed June 3, 2019. Available at: <https://cran.r-project.org/web/packages/survival/citation.html>
- Le Borgne F, Giraudeau B, Querard AH, et al. Comparisons of the performance of different statistical tests for time-to-event analysis with confounding factors: practical illustrations in kidney transplantation. *Stat Med* 2016;35:1103–1116.
- Shu D, Yoshida K, Fireman BH, et al. Inverse probability weighted Cox model in multi-site studies without sharing individual-level data. *Stat Methods Med Res* 2020;29:1668–1681.
- Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed* 2004;75:45–49.
- Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002;21:2175–2197.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
- Gerdts TA, Scheike TH, Andersen PK. Absolute risk regression for competing risks: interpretation, link functions, and prediction. *Stat Med* 2012;31:3921–3930.
- Hogen L, Vicus D, Ferguson SE, et al. Patterns of recurrence and impact on survival in patients with clear cell ovarian carcinoma. *Int J Gynecol Cancer* 2019;29:1164–1169.
- Gandhi AK, Sharma DN, Rath GK, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. *Int J Radiat Oncol Biol Phys* 2013;87:542–548.
- Liu SL, Tinker AV. Omission of adjuvant therapy in stage I clear cell ovarian cancer: review of the BC Cancer experience. *Gynecol Oncol Reports* 2020;31:100533.
- Falzone L, Salomone S, Libra M. Evolution of cancer pharmacological treatments at the turn of the third millennium. *Front Pharmacol* 2018;9:1300.
- Arruebo M, Vilaboa N, Sáez-Gutierrez B, et al. Assessment of the evolution of cancer treatment therapies. *Cancers (Basel)* 2011;3:3279–3330.
- Vijayakumar S, Duggar WN, Packianathan S, et al. Chasing zero harm in radiation oncology: using pre-treatment peer review. *Front Oncol* 2019;9:302.
- Takano M, Sugiyama T, Yaegashi N, et al. Less impact of adjuvant chemotherapy for stage I clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study. *Int J Gynecol Cancer* 2010;20:1506–1510. 10.1111/IGC.0b013e3181fcd089
- Ku FC, Wu RC, Yang LY, et al. Clear cell carcinomas of the ovary have poorer outcomes compared with serous carcinomas: results from a single-center Taiwanese study. *J Formos Med Assoc* 2018;117:117–125.

See JNCCN.org for supplemental online content.

Supplemental online content for:

Adjuvant Treatment of Early Ovarian Clear Cell Carcinoma: A Population-Based Study of Whole Abdominal Versus Pelvic Nodal Radiotherapy

Soumyajit Roy, MBBS; Paul Hoskins, MD, FRCPC; Anna Tinker, MD, FRCPC; Harinder Brar, MD; Gale Bowering, BS; and Gaurav Bahl, MBBS, DNB, FRCPC

J Natl Compr Canc Netw 2021;19(2):172–180

eAppendix 1: Additional Details of Radiotherapy, Surgery, and Follow-Up Policy

eAppendix 2: Sensitivity Analysis Using Flexible Parametric Models

eFigure 1: Evaluable Cohort

eFigure 2: Distribution of Adjuvant Treatment in the Evaluable Cohort

eFigure 3: Adjuvant Treatment Regimens Stratified by Year of Diagnosis

eFigure 4: Cumulative Incidence of Failure in Adjuvant Chemotherapy and Chemoradiotherapy Groups

eFigure 5: Cumulative Censoring for Failure-Free Survival Analysis by Adjuvant Treatment Regimen

eFigure 6: Cumulative Censoring for Overall Survival Analysis by Adjuvant Treatment Regimen

eFigure 7: Cumulative Censoring for Failure-Free Survival Analysis by Radiotherapy Regimen

eFigure 8: Cumulative Censoring for Overall Survival Analysis by Radiotherapy Regimen

eTable 1: Deviation from Standard Treatment Protocol

eTable 2: Flexible Parametric Method for FFS for Adjuvant Chemotherapy Versus ChemoRT

eTable 3: Flexible Parametric Method for OS for Adjuvant Chemotherapy Versus ChemoRT

eTable 4: Flexible Parametric Method for FFS for Adjuvant Chemo-WART Versus Chemo-PRT

eTable 5: Flexible Parametric Method for OS for Adjuvant Chemo-WART Versus Chemo-PRT

eAppendix 1. Additional Details of Radiotherapy, Surgery, and Follow-Up Policy

Details of Whole Abdominal Radiotherapy

Whole abdominal radiotherapy (WART) was initiated 3 weeks after the third cycle of chemotherapy. Pelvic radiotherapy (PRT) was administered first using either a 10 megavolt (MV) or 25 MV linear accelerator to deliver a mid-plane dose of 22.5 Gy in 10 fractions over 2 weeks at 100 cm skin axis distance by parallel opposed fields. The superior margin was placed between fifth lumbar and first sacral vertebra, respectively. The inferior margin was placed at halfway between obturator foramen and ischial tuberosity and the lateral margins at least 1.5 cm lateral to the pelvic brim. This was followed by WART from a 4 MV linear accelerator to deliver a mid-plane dose of 22.5 Gy in 22 fractions over 4.5 weeks at 130 cm skin-source distance. Full posterior kidney shields were used to limit the renal dose to 17 Gy. Patients were treated supine and prone. The superior margin of the field was 1.5 to 2 cm above the diaphragm in quiet expiration. The lower margin matched the lower margin of the pelvic field. Lateral margins encompassed the widest portion of the iliac crests ensuring that the bowel shadows seen on stimulation were covered. Triangular blocks were used with a line drawn from the anterior superior iliac spine, inferomedially with a margin of 1.0 to 1.5 cm lateral from the obturator foramen.

Details of PRT

In the chemotherapy-PRT (chemo-PRT) group, radiotherapy protocol included external-beam radiotherapy to pelvis to a total dose of 45 Gy in 25 fractions over 5 weeks starting at 3 to 4 weeks after the third cycle. The target volume for PRT included common iliac (from interspace between 4th and 5th lumbar vertebrae), external and internal iliac, obturator and presacral group (up to the interspace between second and third sacral vertebrae) of lymph nodes. Traditionally PRT was delivered using 3D conformal technique using coplanar 4-field beam (anterior, posterior, and 2 lateral portals) arrangement with megavolt photons. However, treatment techniques evolved over time with use of intensity-modulated radiotherapy and volumetric modulated arc therapy for delivering PRT.

Pelvic and Para-Aortic Lymphadenectomy

The standard, uniformly applied surgery consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, washings, and removal of suspicious nodes. Routine pelvic and/or para-aortic lymphadenectomy was not mandated. Approximately 36.5% patients (n=23) in the chemotherapy (chemo) group versus 35.5% (n=17) in the chemo-WART group and 40% (n=17) in the chemo-PRT group had complete lymphadenectomy. There was no difference in the proportion of patients who underwent complete lymphadenectomy among the 3 treatment groups ($P=.87$).

Follow-Up Policy

Clinical assessments including history and physical examination (including nodal areas, chest, abdomen, bimanual pelvic, and rectal examination) were repeated at 4 monthly intervals for the first 2 years after treatment completion, every 6 months for the next 3 years, and annually thereafter. Routine tumor markers and imaging were not needed during follow-up visits, unless indicated by symptoms or signs on examination.

eAppendix 2. Sensitivity Analysis Using Flexible Parametric Models

Flexible parametric models were constructed to identify treatment-effect on overall survival (OS) and failure-free survival (FFS) adjusted for covariables (age at diagnosis, risk group, cancer stage, and year of diagnosis) and time (see supplemental eTables 2–5). Best fit model was identified using second-order Akaike's information criterion (AIC), with lower AIC indicating superior goodness of fit.

eFigure 1. Evaluable cohort.

eFigure 2. Distribution of adjuvant treatment in the evaluable cohort.
Abbreviations: chemo, chemotherapy; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

eFigure 3. Adjuvant treatment regimens stratified by year of diagnosis.

Abbreviations: chemo, chemotherapy; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

eFigure 4. Cumulative incidence of failure in adjuvant chemotherapy and chemoradiotherapy groups.

Cumulative number of censoring											
Chemotherapy	0	2	6	8	9	11	17	18	21	22	22
Chemoradiotherapy	0	4	15	22	24	29	35	35	35	37	39
	0	1	2	3	4	5	6	7	8	9	10
Year											

eFigure 5. Cumulative censoring for failure-free survival analysis by adjuvant treatment regimen.

Cumulative number of censoring											
Chemotherapy	0	2	5	7	8	10	15	17	18	20	20
Chemoradiotherapy	0	3	14	19	22	28	33	33	33	34	36
	0	1	2	3	4	5	6	7	8	9	10
Year											

eFigure 6. Cumulative censoring for overall survival analysis by adjuvant treatment regimen.

Cumulative number of censoring											
Chemo-WART	0	0	1	4	4	6	9	9	9	11	12
Chemo-WART	0	4	14	18	20	23	26	26	26	26	27
	0	1	2	3	4	5	6	7	8	9	10
Year											

eFigure 7. Cumulative censoring for failure-free survival analysis by radiotherapy regimen.
Abbreviations: chemo, chemotherapy; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

Cumulative number of censoring											
Chemo-WART	0	0	0	1	1	4	5	5	5	6	7
Chemo-PRT	0	3	14	18	21	24	28	28	28	28	29
	0	1	2	3	4	5	6	7	8	9	10
Year											

eFigure 8. Cumulative censoring for overall survival analysis by radiotherapy regimen.
Abbreviations: chemo, chemotherapy; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

eTable 1. Deviation From Standard Treatment Protocol

Adjuvant Treatment Regimen	n (%)
Chemotherapy	
Cisplatin/Etoposide × 6	1 (1.6)
Cisplatin/Etoposide × 3 followed by carboplatin/paclitaxel × 3	2 (3.2)
Carboplatin/Paclitaxel × 3	1 (1.6)
Cisplatin × 6	5 (8.0)
Cisplatin/Cyclophosphamide × 6	7 (11.2)
Cisplatin × 1 followed by carboplatin × 5	2 (3.2)
Cisplatin × 2 followed by carboplatin × 4	1 (1.6)
Carboplatin × 6	5 (8.0)
Chemo-WART	
Cisplatin/Cyclophosphamide × 6	6 (12.5)
Cisplatin/Etoposide × 3	6 (12.5)
Only PRT to 50 Gy in 25 fractions	1 (2.1)
Dose reduction in the abdominal phase of WART	4 (8.4)
Deferred WART after paclitaxel/carboplatin × 3	1 (2.1)
Chemo-PRT	
Cisplatin/Paclitaxel × 6	1 (2.3)
Carboplatin × 3	1 (2.3)
Carboplatin × 6	1 (2.3)
PRT to a total dose of 40 Gy in 20 fractions	1 (2.3)
PRT to a total dose of 50.4 Gy in 28 fractions	3 (6.9)

Abbreviations: Chemo, chemotherapy; PRT, pelvic nodal radiotherapy; RT, radiotherapy; WART, whole abdominal radiotherapy.

eTable 2. Flexible Parametric Method for FFS for Adjuvant Chemotherapy Versus ChemoRT^a

Variable	Adjusted HR ^a (95% CI)
Age at diagnosis	0.99 (0.96–1.01)
Risk group	
Group 2/cytology negative	Ref
Group 1/cytology positive	2.66 (1.21–5.87)
Treatment group	
Chemotherapy	Ref
ChemoRT	0.56 (0.34–0.93)
Cancer stage (FIGO 1988)	
IC	Ref
IIA/IIB	0.82 (0.21–3.12)
IIC	0.83 (0.47–1.47)
Year of diagnosis	
1984–1994	Ref
1995–2004	0.76 (0.39–1.50)
2005–2015	1.15 (0.63–2.08)

Abbreviations: ChemoRT, chemoradiotherapy; FFS, failure-free survival; HR, hazard ratio.

^aFlexible parametric model with 3 *df*.

^bBold indicates statistically significant *P* value.

eTable 3. Flexible Parametric Method for OS for Adjuvant Chemotherapy Versus ChemoRT^a

Variable	Adjusted HR (95% CI)
Age at diagnosis	1.01 (0.99–1.03)
Risk group	
Group 2/cytology negative	Ref
Group 1/cytology positive	1.80 (0.96–3.38)
Treatment group	
Chemotherapy	Ref
ChemoRT	0.69 (0.43–1.11)
Cancer stage (FIGO 1988)	
IC	Ref
IIA/IIB	0.62 (0.20–1.87)
IIC	0.78 (0.44–1.36)
Year of diagnosis	
1984–1994	Ref
1995–2004	0.80 (0.43–1.48)
2005–2015	1.64 (0.90–2.99)

Abbreviations: ChemoRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival.

^aFlexible parametric model with 4 *df*.

eTable 4. Flexible Parametric Method for FFS for Adjuvant Chemo-WART Versus Chemo-PRT^a

Variable	Adjusted HR ^b (95% CI)
Age at diagnosis	1.00 (0.97–1.04)
Risk group	
Group 2/cytology negative	Ref
Group 1/cytology positive	5.94 (1.54–22.9)
Treatment group	
Chemo-WART	Ref
Chemo-PRT	1.43 (0.44–4.70)
Cancer stage (FIGO 1988)	
IC	Ref
IIA/IIB	2.12 (0.33–13.6)
IIC	0.33 (0.12–0.94)
Year of diagnosis	
1984–1994	Ref
1995–2004	2.51 (0.36–17.4)
2005–2015	1.61 (0.24–10.8)

Abbreviations: Chemo, chemotherapy; FFS, failure-free survival; HR, hazard ratio; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

^aFlexible parametric model with 4 *df*.

^bBold indicates statistically significant *P* value.

eTable 5. Flexible Parametric Method for OS for Adjuvant Chemo-WART Versus Chemo-PRT^a

Variable	Adjusted HR (95% CI)
Age at diagnosis	0.98 (0.93–1.04)
Risk group	
Group 2/cytology negative	Ref
Group 1/cytology positive	6.90 (0.71–17.05)
Treatment group	
Chemo-WART	Ref
Chemo-PRT	1.75 (0.67–4.02)
Cancer stage (FIGO 1988)	
IC	Ref
IIA/IIB	0.49 (0.10–2.37)
IIC	0.59 (0.25–1.40)
Year of diagnosis	
1984–1994	Ref
1995–2004	1.75 (0.67–4.54)
2005–2015	1.89 (0.55–6.47)

Abbreviations: Chemo, chemotherapy; HR, hazard ratio; OS, overall survival; PRT, pelvic nodal radiotherapy; WART, whole abdominal radiotherapy.

^aFlexible parametric model with 5 *df*.