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Original Article

Treatment Outcomes and Toxicity Profiles with PORTEC-3 Trial Regimen in South Asian Cohort of High-Risk Endometrial Cancer Patients: A Single-Center Ambispective Analysis

Parth Verma[1] Rajasree Rajan[1] Ajay Sasidharan[1] Sruthi Kalavagunta[1] Debnarayan Dutta[1] Beena Kunheri[1] Neethu Kunnath[2] Priya Bhati[2] Anupama Rajanbabu[2] Indu Nair[3] Rakesh Moolayil Puthenveedu[4] Nikhil Haridas[4] Wesley Jose[4] Keechilat Pavithran[4]

[1] Department of Radiation Oncology, Amrita Institute of Medical Sciences, Kochi, India
[2] Department of Gynec Oncology, Amrita Institute of Medical Sciences, Kochi, India
[3] Department of Pathology, Amrita Institute of Medical Sciences, Kochi, India
[4] Department of Medical Oncology, Amrita Institute of Medical Sciences, Kochi, India

Address for correspondence Ajay Sasidharan, MD, DNB, FRCR, Department of Radiation Oncology, Amrita Institute of Medical Sciences, Kochi 682041, India (e-mail: ajays.ganga@gmail.com).

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Abstract

Ajay Sasidharan

Objectives Adjuvant chemoradiation followed by chemotherapy is the current standard of care in high-risk endometrial cancer after the PORTEC-3 trial. There is a lack of data on this treatment regimen in the South Asian patient cohort. The present study aims to assess toxicity profiles and outcomes in this cohort of patients.

Materials and Methods High-risk endometrial cancer patients planned for adjuvant chemoradiation followed by chemotherapy were included. Toxicity was graded using the Radiation Therapy Oncology Group and Common Terminology Criteria for Adverse Events criteria. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. Cox regression analysis was done to find out the predictors of DFS.

Results This study included 58 patients treated from October 2016 to August 2022. Median age was 61 years (interquartile range [IQR] 56–66), with Fédération Internationale de Gynécologie et d'Obstétrique Stages I = 26 (44.8%), II = 5 (8.6%), and III = 27 (46.6%). p53 positivity was seen in 38 (65.5%) patients. Intensity-modulated radiotherapy was used in 44 (79.3%) patients. There was no treatment discontinuation during chemoradiation. Acute Grade 2 and above toxicity during chemoradiation were diarrhea in 10 (17.2%) and hematological in 2 (3.4%). For the planned adjuvant chemotherapy in 55 patients, 51 (92.7%) completed four cycles. Grade 2 or above neuropathy was seen in 11 (20%), with 5 (9%) having persisting neuropathy at 1-year follow-up. At a median follow-up of 31 months, 15 (25.8%) patients recurred; distant

Keywords
- endometrial cancer
- high risk
- outcome
- South Asian
- toxicity

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= 13 and isolated para-aortic = 2. The median time to recurrence was 16 months (IQR 12–22), with 80% (12 out of 15) of recurrence within the first 2 years of follow-up. The actuarial 5-year DFS and OS were 63.8 and 76.5%, respectively. In univariate analysis, p53 positivity and lymphovascular space invasion were predictors for DFS, with *p*-values 0.031 and 0.027, respectively. There was no significant predictor identified in multivariate analysis.

Conclusion There is good tolerance and compliance to adjuvant chemoradiation and chemotherapy in this South Asian cohort of patients with high-risk endometrial cancer, with no toxicity-related treatment breaks during radiation. The majority of the recurrences were seen at distant sites and within the first 2 years of follow-up. These findings are in line with the outcomes of the PORTEC-3 trial.

Introduction

The incidence of endometrial cancers has been increasing worldwide, particularly in South Asian countries such as India, with GLOBOCAN 2020 estimating 16,413 new cases in 2020.[1] The prognosis for patients with endometrial cancer largely remains favorable, except among the patients with high-risk prognostic categorization.

Since the publication of the results of the PORTEC-3 trial, concurrent chemoradiation followed by adjuvant chemotherapy has been the standard of care in high-risk endometrial cancer.[2–4] However, the study only included women from North American, Western European, and Australian regions, and extrapolation of treatment outcomes and toxicities to other ethnic populations may be fraught with pitfalls. The data assessing toxicity and outcomes among women with endometrial cancer from South Asian countries who have been treated with the PORTEC-3 treatment regimen are lacking, with there being an assumption of poorer tolerance to the treatment regimen due to various causes. The present study aims to assess toxicity profiles and outcomes in this cohort of patients.

Materials and Methods

Patients with high-risk endometrial cancer treated with the PORTEC-3 trial regimen between October 2016 and August 2022 were included in this ambispective analysis. All patients underwent staging surgery, either at the same institute or from other referring centers, following which they were initiated on adjuvant treatment at our center. The decision regarding modality of surgery (robotic, laparoscopic, or open) and lymph node dissection was made by the concerned surgeons. Patients were staged using Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) 2009 staging for endometrial cancers. After case discussion in the institutional multidisciplinary tumor board, patients with Eastern Cooperative Oncology Group performance status (PS) 0 to 2 falling under the high-risk stratification for carcinoma endometrium were offered adjuvant treatment as per the PORTEC-3 trial regimen. High risk was defined as Stage III or p53 positive or nonendometrioid histology. Patients were assessed for adequacy of cardiac, bone marrow, liver, and renal function before treatment. Patients with uterine sarcomas or carcinosarcomas, history of prior chemotherapy or pelvic irradiation, ≥R1 resection, and irritable bowel disease were excluded. Adjuvant treatment was initiated preferably <6 weeks from surgery, but no later than 8 weeks. Patients were treated with external beam radiation therapy (RT) to a dose between 45 and 48.6 Gy in 1.8 Gy fractions, 5 days a week. The clinical target volume included the proximal 3 to 4 cm of the vagina, parametrial tissues, and internal, external, and common iliac lymph node regions up to the aortic bifurcation. The clinical target volume was extended to include the lower para-aortic region for upper common iliac nodal involvement and to include the higher para-aortic region in case of para-aortic involvement (with a margin of ≥ 2 cm above the highest involved lymph node. Following external beam therapy, patients with cervical involvement were treated with brachytherapy boost to the vaginal vault. Brachytherapy was delivered using a high dose rate (HDR) to a dose of 12 Gy in two fractions of 6 Gy each prescribed to 5 mm from the vaginal surface to the upper 3 to 4 cm of the vagina. Radiation was delivered with either intensity-modulated radiotherapy (IMRT) in Accuray Radixact X9 or TomoH, or with three-dimensional conformal radiotherapy (RT) in Elekta Precise Digital or Synergy Platform. Image-guided HDR brachytherapy was delivered using the Nucletron HDR machine. Overall RT treatment time was not to exceed 50 days. Concurrent chemotherapy was given with two cycles of intravenous cisplatin 50 mg/m^2 followed by four cycles of intravenous paclitaxel (175 mg/m^2) and carboplatin (area under the curve [AUC] 5–6) at 21-day intervals. Chemotherapy dose reduction of ≥ 25% and deferral was documented. The follow-up schedule was 3 monthly for the first 2 years, 6 monthly for 5 years, and yearly thereafter. Acute and late toxicity was graded using Radiation Therapy Oncology Group (RTOG) criteria and Common Terminology Criteria for Adverse Events v5.0.

Statistical Analysis

All analyses were performed with the use of statistical software (SPSS Statistics for Windows, version 21.0; IBM

Corporation). Kaplan–Meier method was used to estimate disease-free survival (DFS) and overall survival (OS). OS was calculated from the date of surgery to the date of the last follow-up or death. PFS was calculated from the surgery date to progression date (progression was defined as radiological or clinical progression). Univariate (log-rank test) and multivariate analyses (Cox proportional hazard model) were performed for factors affecting DFS.

Results

Fifty-eight patients with high-risk endometrial cancer were included (median age = 61 years, range 35–81) and their characteristics are shown in ►Table 1. The median time between the onset of symptoms and the patient presenting to a hospital was 4 weeks (interquartile range [IQR] 2–12 weeks). Staging surgery was performed using robotic (33, 56.9%), laparoscopic (9, 15.5%), and open (16, 27.6%) methods. Forty-eight patients (83%) underwent staging surgery at our center, while 10 (17%) were referred to our center for adjuvant treatment. FIGO (2009) Stage I = 26 (25%), Stage II = 5 (8%), and Stage III = 27 (46.5%) patients. Serous carcinoma was 15 (26%), and endometrioid carcinoma was 29 (50%). Molecular classification with p53 positive was 38 (65.5%) and p53 negative was 20 (34.5%). All 15 serous carcinomas and 1 poorly differentiated were p53 positive. Out of 29 endometrioid carcinomas, 13 were p53 positive and 16 were p53 negative. Out of seven clear cell carcinomas, five were p53 positive, two were p53 negative, and among six papillary histology, four were p53 positive and two were p53 negative.

Table 1 Distribution of various patient, disease, and treatment-related factors

Parameter	*n* (%)
Age, y	
< 60	22 (38%)
60–69	28 (48%)
≥70	8 (14%)
FIGO staging (as per FIGO 2009 staging)	
IA	14 (24.1%)
IB	12 (20.7%)
II	5 (8.6%)
IIIA	12 (20.7%)
IIIC1	11 (18.9%)
IIIC2	4 (7%)
Histology	
Endometroid	29 (50%)
Serous	15 (26%)
Clear cell	7 (12%)
Papillary	6 (10.3%)
Poorly differentiated	1 (1.7%)
Type of endometrial cancer	
Type 1	18 (31%)
Type 2	40 (69%)
Grade	
Low grade	16 (18%)
High grade	42 (72%)
Myometrial invasion	
< 50%	24 (41%)
≥50%	34 (59%)
LVSI	
LVSI positive	34 (57%)
LVSI negative	24 (43%)
P53	
p53 positive	38 (65.5%)
p53 negative	20 (34.5%)
Staging surgery	
Robotic	33 (56.9%)
Laparoscopic	9 (15.5%)
Open	16 (27.6%)
Lymph node sampling	
Sentinel lymph node biopsy	36 (62%)
Pelvic lymph node dissection	10 (17%)
Pelvic lymph node dissection + para-aortic sampling	1 (2%)
Pelvic + para-aortic dissection	7 (12%)
Not assessed	4 (7%)
Radiation modality	
IMRT	46 (79%)
3DCRT	12 (21%)

Abbreviations: FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; IMRT, intensity-modulated radiotherapy; LVSI, lymphovascular space invasion; 3DCRT, three-dimensional conformal radiotherapy.

All 58 patients received RT. 18 (31%) patients received an intravaginal brachytherapy boost. Of the patients offered adjuvant therapy, one patient did not consent to chemotherapy (both concurrent and adjuvant), one patient did not consent to adjuvant chemotherapy, and the remaining 56 (98%) received chemoradiation and chemotherapy as shown in ►Fig. 1.

The most common adverse effect during chemoradiation was increased frequency of bowel movements (38 patients, 65.5%), and 28 of those were Grade 1 and did not require medications. Grade 2 diarrhea requiring parasympatholytic drugs was seen in 10 (17.2%) patients. Grade 2 or higher hematological toxicities were noted in only two (3.4%)

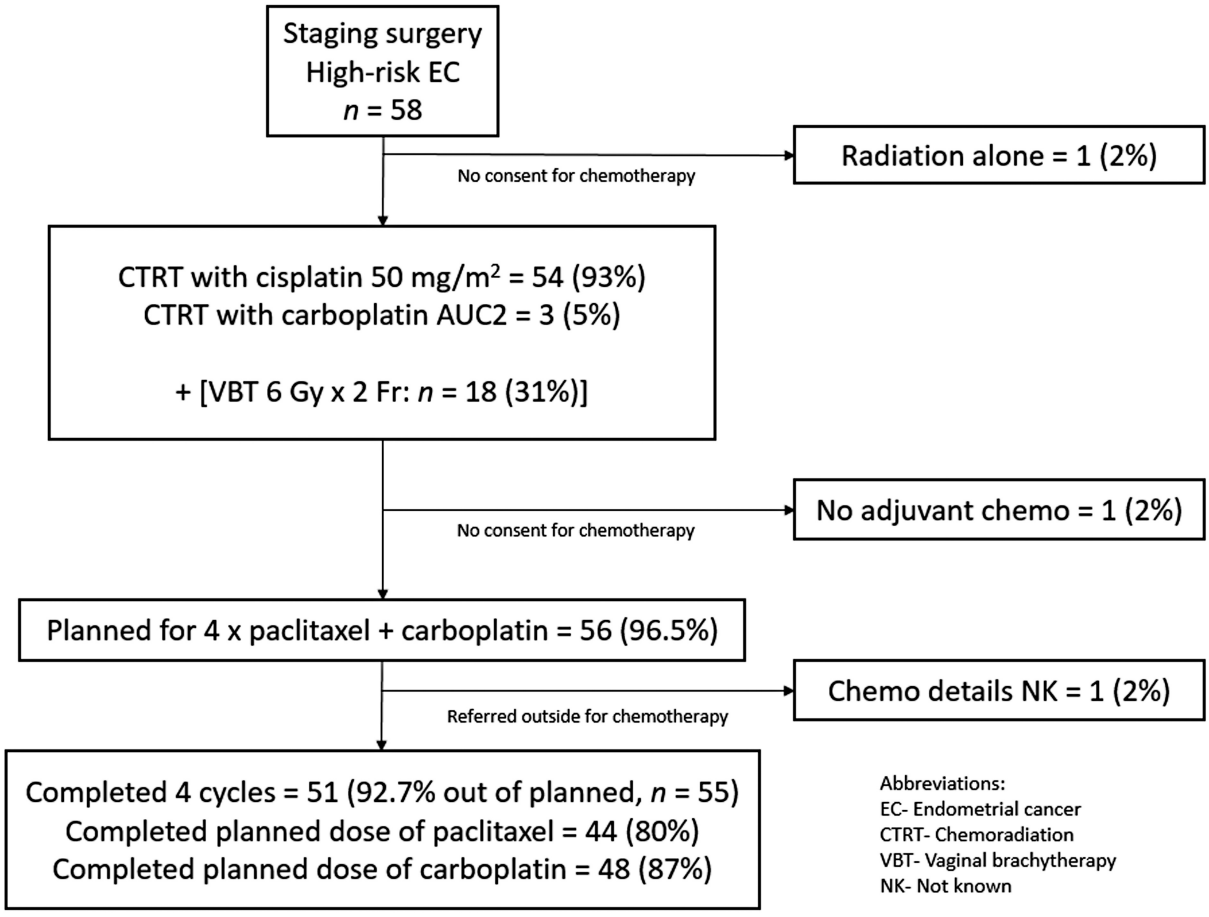

Fig. 1 Consort diagram. CTRT, chemoradiation; EC, endometrial cancer; NK, not known; VBT, vaginal brachytherapy.

patients, while no Grade 2 or above genitourinary (GU) toxicities were seen. There were no treatment discontinuations during radiation. One patient received a single cycle of cisplatin, the second dose was skipped due to Grade 4 hyponatremia; one had dose adjustment due to weight loss in the second cycle (first cycle 70 mg and second cycle 60 mg), while three had received concurrent carboplatin because of cardiac comorbidities.

One patient had adjuvant chemotherapy at a different center and information was not available. Of the 55 patients planned for adjuvant chemotherapy at our center, 7 (12.5%) were initiated with a reduced dose (paclitaxel at 135 mg/m^2 or carboplatin at AUC 4) due to a poor anticipated tolerance (elderly or PS 2 or high creatinine or cardiac comorbidities). All seven had paclitaxel dose reduction, while four had carboplatin dose reduction alone, with two of them receiving a standard dose of paclitaxel from the second cycle onward. Chemotherapy with the standard dose was planned for 48 (87.5%). Overall, 14 patients developed peripheral neuropathy, with 11 Grade 2 or above requiring medication. The patient who received only a single cycle of concurrent cisplatin received a fifth dose of adjuvant chemotherapy with paclitaxel and carboplatin.

While 51 (92.7%) out of planned 55 patients completed four cycles of adjuvant chemotherapy, 6 (11%) required dose reduction due to toxicity (3 required dose reduction for paclitaxel, 2 for both paclitaxel and carboplatin, and 1 required dose reduction for carboplatin) because of toxicity. Among four patients who did not complete four cycles of chemotherapy, one had a dose reduction in the third cycle for paclitaxel, and the fourth cycle was deferred. The remaining three patients' chemotherapy was deferred totally after one, two, and three cycles of chemotherapy, respectively, in each of these patients. Of the seven (12.5%) patients initiated on dose-reduced chemotherapy, two patients required further dose reduction for paclitaxel, while no further dose reduction was needed for carboplatin; six completed four cycles of chemotherapy, while one completed three cycles of chemotherapy. Paclitaxel with the planned dose was completed by 44 (80%) patients, and adjuvant carboplatin with the planned dose was received by 48 (87%) patients. Overall dose reduction was done for paclitaxel in 12 (21.8%) patients and for carboplatin in 7 (12.7%).

At a median follow-up of 31 months (IQR: 19–42), 1 patient was lost to follow-up, 15 patients had relapsed, and 5 patients had expired (3 with relapse, 2 due to other causes). Isolated para-aortic relapse was seen in 2 patients, 13 patients had distant metastases with 1 patient having combined para-aortic and distant relapse. Both patients with isolated para-aortic relapse were high grade, p53 positive,

lymphovascular space invasion (LVSI) positive, with initial Stages IB and IIIC1. Among 11 Stage IIIC1 patients, 1 (9%) had isolated para-aortic relapse, and this patient had bilateral external iliac nodes at baseline. Distant relapse sites included nodes ($n = 8/12$; 67%), lung ($n = 7/12$; 58%), liver ($n = 2/12$; 17%), peritoneum ($n = 2/12$; 17%), and skeletal, adrenal, and abdominal wall ($n = 1$ each).

In univariate analysis, LVSI ($p = 0.027$) and p53 status ($p = 0.031$) were significant factors affecting DFS, while significance was not seen in multivariate analysis as shown in ►Table 2. Among 20 p53-negative patients, 2 had a distant relapse, while among 38 p53-positive patients, 11 had a distant relapse and 2 had isolated para-aortic relapse. Among the 15 relapsed patients, 13 were p53 positive (9 LVSI positive and 4 LVSI negative) and 2 were p53 negative (1 LVSI positive and 1 LVSI negative). At 2 and 5 years, OS rates were 92.2 and 86%, while DFS rates were 76.5 and 63.8% as given in ►Fig. 2. At 2 and 5 years, the DFS for p53-positive versus -negative patients were 66.07 versus 94.74% ($p = 0.031$), and LVSI-positive versus -negative patients were 61.3 versus 89.1% ($p = 0.027$) as shown in ►Fig. 3.

While no Grade 2 and above late GU toxicities were seen, one patient underwent surgery for bowel obstruction due to adhesions and incisional hernia, and one had Grade 2 frequency of bowel movements. Grade 2 or above neuropathies that required medication were seen in 11 (20%) patients (Grade 2 = 7; Grade 3 = 4) after adjuvant chemotherapy, with 5 (9%) having persistent significant neuropathy after 1-year follow-up. The toxicity profile during chemoradiation and chemotherapy is shown in ►Table 3.

Table 2 Factors affecting DFS

Factor	*N*	2-yDFS	5-y DFS	*p*-Value (univariate analysis)	*p*-Value (HR) (multivariate analysis)
Age (y)					
>60	30	71.0%	52.6%	0.511	–
≤60	28	76.9%	76.4%		
FIGO 2009 stage					
Stage III	27	71.3%	64.8%	0.757	–
Stages I–II	31	76.4%	NR		
Histology					
Nonendometrioid	28	66.0%	51.7%	0.123	–
Endometrioid	30	88.1%	71.8%		
Grade					
Grade 3	42	85.7%	73.4%	0.248	–
Grades 1–2	16	76.7%	56.1%		
LVSI					
LVSI positive	24	61.3%	53.6%	0.027	0.071 (HR = 2.714; 95% CI: 0.917–8.031)
LVSI negative	34	89.1%	72.0%		
p53 status					
p53 positive	20	66.0%	50.82%	0.031	0.079 (HR = 3.850; 95% CI: 0.856–17.317)
p53 negative	38	94.7%	84.2%		
Type of surgery					
Robotic/laparoscopy	42	81.4%	54.0%	0.541	–
Open	16	64.6%	NR		
Technique of RT					
IMRT	46	78.6%	64.5%	0.976	–
3DCRT	12	75.6%	NR		
Adjuvant chemotherapy					
Planned dose four cycles	38	71.1%	53.6%	0.087	–
Dose reduced/ no chemotherapy	20	88.5%	NR		

Abbreviations: CI, confidence interval; DFS, disease-free survival; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; LVSI, lymphovascular space invasion; NR, not reported; 3DCRT, three-dimensional conformal radiotherapy.

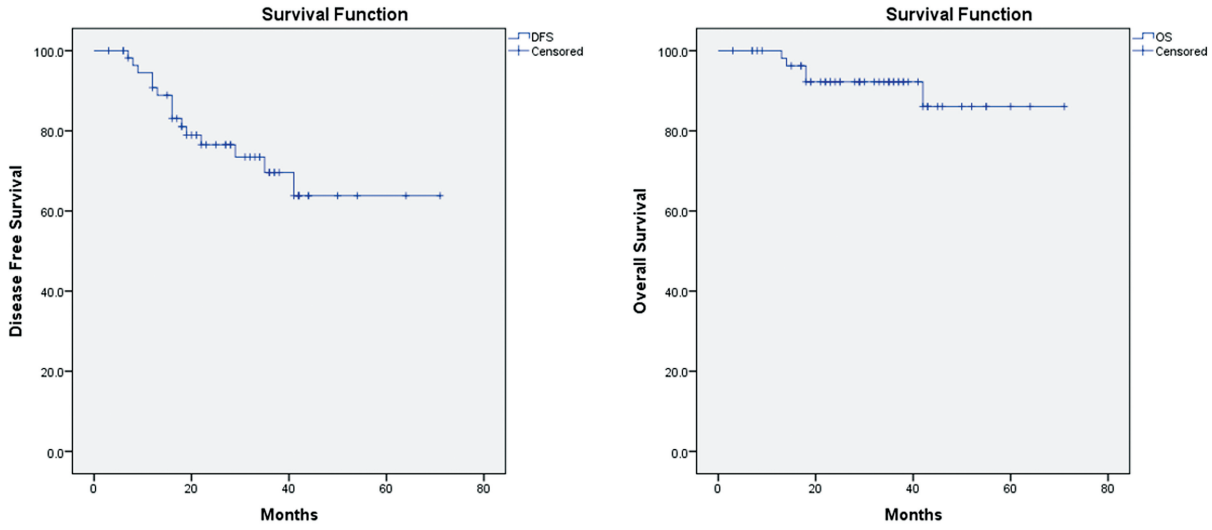

Fig. 2 Kaplan–Meier method for disease-free survival and overall survival.

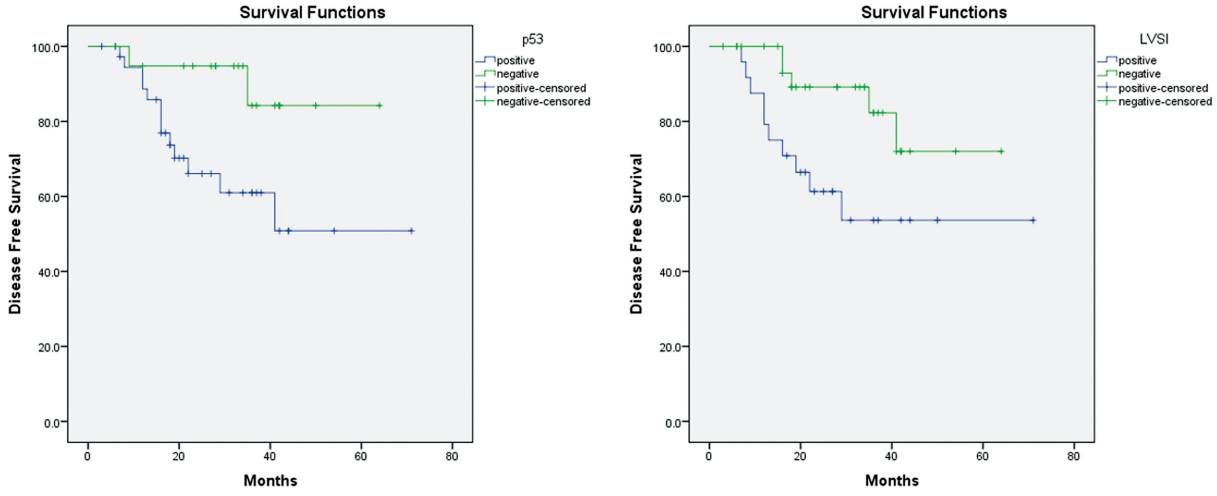

Fig. 3 Kaplan–Meier curves for disease-free survival with p53 and lymphovascular space invasion (LVSI) status.

Table 3 Grade 2 and above toxicities

Toxicity	Chemoradiation ($n = 58$)	Adjuvant chemotherapy ($n = 55$)	Late toxicities ($n = 55$)
Gastrointestinal	10 (17.2%)	–	2 (3.6%)
Genitourinary	Nil	–	–
Hematological	2 (3.4%)	15 (27.3%)	–
Neuropathy	–	11 (20%)	5 (9%)

Discussion

RT alone has been the adjuvant treatment in high-risk endometrial cancer for decades. With distant relapse being the most common, the role of chemotherapy was established as it improved progression-free survival and OS. A phase III Japanese trial showed that adjuvant chemotherapy may be an alternative to radiation in intermediate to high-risk endometrial cancer.[5] In the Gynecologic Oncology Group (GOG) 122[6] trial, whole abdominal irradiation (WAI) 30 Gy followed by a 15-Gy boost was compared with doxorubicin–cisplatin chemotherapy, with a better progression-free survival seen with chemotherapy. However, more than half of the patients in both arms had relapsed and avoidance of RT resulted in a higher incidence of pelvic and abdominal recurrences. Importantly, the treatment completion rate was higher in radiation—84% with radiation and 63% with

chemotherapy, and toxicity rates were 3% in the WAI arm against 17% in the chemotherapy arm. Of the five patients who expired while on treatment, four were in the chemotherapy arm (although the cause of death was not mentioned). Neuropathies were noted in 42 (22%) out of 191 patients with the AP regimen. When chemotherapy is given alone, locoregional recurrence approaches 20%, hence a combined modality approach was selected as the experimental arm in the PORTEC-3 trial regimen, with prior studies RTOG 9708[7] and GOG 184[8] trials showing feasibility and efficacy for the combined approach.[2] The updated analysis showed significantly improved OS and progression-free survival with chemoradiotherapy versus RT alone for Stage III and serous histology. The 5-year failure-free survival for serous histology was 59.7 versus 47.9% ($p = 0.008$) and for Stage III was 70.9 versus 58.4% ($p = 0.011$). A combined modality approach with four cycles of combination chemotherapy and adding radiation with concurrent chemotherapy reduces both distant and locoregional recurrences and has low rates of manageable independent toxicities of both chemotherapy and radiation.

GOG-258[9] tested the hypothesis of whether the addition of two more cycles of high-dose paclitaxel–carboplatin and avoiding RT is associated with superior relapse-free survival compared with chemoradiation. The patterns of relapse at 60 months were similar to previous trials, with higher pelvic and para-aortic recurrences in the chemotherapy-alone arm (2 and 11% in the CTRT arm, against 7 and 20% in the chemotherapy-alone arm, respectively), and while the chemotherapy-alone arm had fewer distant recurrences, the difference was narrow (27 vs. 21%). Although the patient-reported trial outcome index score was marginally higher for the chemotherapy-alone arm, it failed to exceed the six-point difference which was set as being clinically relevant. The patient-reported neuropathy scores, however, were worse in the chemotherapy-alone arm. The updated results of the trial[11] mention 134 deaths in the chemoradiation arm against 125 in the chemotherapy-alone arm; however, no data regarding patient-reported quality of life (QOL) outcomes were made available.

The results from the GOG-258 trial have led to interest in increasing the adjuvant combination chemotherapy cycles from four to six, and even omission of RT in the management of high-risk endometrial cancer. In a Surveillance, Epidemiology, and End Results review, Garg et al showed that for patients with Stage IIIC disease, the 5-year DFS drops to 47% when extranodal involvement was present.[10] And many suggest chemotherapy upfront or alone for such patients. However, the omission of RT has consistently led to increased locoregional relapses. Additionally, there was an increased rate of peripheral neuropathies with six versus four cycles of taxane-based chemotherapy. Although alternating sequencing protocols are often used,[12] including giving chemotherapy upfront or sandwiching RT in between cycles of chemotherapy[13] citing better tolerance to treatment, there are no large randomized comparisons between such schedules to give us a definite answer. The recent randomized trial comparing the sandwich regimen to chemoradiation was closed early but suggested worse tolerance with the sandwich regimen.[14] Also, a multi-institutional analysis of adjuvant chemotherapy and radiation sequence in women with Stage IIIC endometrial cancer did not show any difference in DFS or OS.[15] The population-based study of 1,241 patients from the Netherlands also showed adjuvant radiation plus chemotherapy was associated with improved OS than chemotherapy or radiation alone in FIGO Stage IIIC cancers.[13] Adjuvant RT and chemotherapy combination was shown to improve outcomes in Stage IIIC cancer by Secord et al.[16]

This report on a South Asian cohort of high-risk endometrial cancer patients details the outcome and toxicity profile after treatment with the PORTEC-3 treatment regimen. There is good treatment compliance in our cohort of patients and comparable to the original trial population. Out of the 55 planned for adjuvant chemotherapy, 51(93%) completed four cycles. Paclitaxel with the planned dose was completed by 44 patients (80%, against 71%) and carboplatin with the planned dose was received by 48 women (87%, against 79%). The dose reduction rate for carboplatin of 12.7% was comparable to the original trial's 11%. The dose reduction rate for paclitaxel at 21.8% appears to be higher than in the original trial population rate of 15%. In terms of outcomes, the estimated 5-year OS and DFS observed in our study are lower compared with the original trial (OS 76.5 vs. 81.4% and DFS 63.8 vs. 76.5%). Compared with the original trial, although there was no difference in the proportion of stage, there was a higher proportion of patients with p53 positive (65.5 vs. 23%) in our cohort, which might be a factor for the overall inferior outcome. The 5-year DFS and OS were 48 and 54% for p53 abnormal endometrial cancer in the updated molecular risk stratified PORTEC-3 analysis,[17] although they benefited with the addition of chemotherapy.

There were no toxicity-related treatment breaks during radiation. Concurrent cisplatin was completed by 54 patients (93%, against 92% in the original trial). Wortman et al evaluated treatment-related toxicities in the PORTEC-3 patients, and in the 15% of patients who received IMRT, there were fewer $\geq$ Grade 2 adverse events during and after treatment.[18] The RTOG 1203 study has shown pelvic IMRT is associated with significantly less gastrointestinal and urinary toxicity than standard RT. The use of IMRT was higher in our cohort with 79% being treated with IMRT.[19]

Strengths of the study include the selection of a high-risk subgroup as per the ESGO/ESTRO/ESP guideline which is relevant to the current management as per molecular risk stratification, in the South Asian cohort of patients. A uniform treatment protocol has been maintained throughout the study period. Tolerance to the treatment regimen is also shown in this cohort with toxicity rates comparable to the Western population, with dose reductions used as clinically thought significant.

There are a few limitations to this study: (1) the ambispective nature of data collection and (2) the small sample size. Other limitations include the lack of status of Mismatch repair (MMR) genes and DNA polymerase epsilon (POLE) mutation status. Risk stratification was based on stage, grade, aggressive histology, and p53 status alone. It was not a practice to

categorize LVSI as substantial or focal during the period of this study. The small sample size and number of events in the study limit the interpretation of predictors affecting the outcome and toxicity profile. Patient-reported QOL questionnaires could also have added value to the toxicity evaluation in the study, which is planned for a prospective evaluation henceforth in subsequent cohorts of patients.

Conclusion

There is good tolerance and compliance to adjuvant chemoradiation and chemotherapy in this South Asian cohort of patients with high-risk endometrial cancer, with no toxicity-related treatment breaks during radiation. There is a high rate of locoregional control with the majority of relapse being distant and within the first 2 years of follow-up. These findings are in line with the outcomes of the PORTEC-3 trial.

Note

The abstract of this study was accepted by ESMO Gynaecological Cancers Congress, and won the best poster award in the category: Endometrial cancer, and was published in the ESMO Open. DOI: https://doi.org/10.1016/j.esmoop.2023.100798

Authors' Contribution

P.V., R.R., A.S., and S.K. did data collection, statistical analysis, and drafted the manuscript; D.D. and B.K. participated in the design, supervision of the study and treatment; N.K., P.B., A.R.B., and I.N. were involved in the supervision of the treatment and the study; R.M.P. and W.J. involved in the design, supervision of the treatment, and drafting the manuscript; N.H. and P.K. involved in the supervision of the treatment and the study; all authors read and approved the final manuscript.

Ethical Approval and Declaration of Helsinki

This study is observational. The Amrita Institute of Medical Sciences Institutional ethics committee has confirmed that no ethical approval is required. I/We confirm that this ambispective analysis conforms to the ethical norms and standards in the Declaration of Helsinki.

Conflict of Interest

None declared.

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