Original Article

Pattern of care in operable endometrial cancer treated at a rural-based tertiary care cancer center

Dessai SB, Adrash D, Geetha M[1], Arvind S[2], Bipin J, Nayanar S[2], Sachin K, Biji MS[3], Balasubramanian S

Departments of Surgical Oncology, [1]Radiation Oncology and [3]Palliative Medicine, Malabar Cancer Center, [2]Department of Clinical Laboratory Services and Translational Research, Division of Oncopathology, Malabar Cancer Center, Kannur, Kerala, India

Correspondence to: Dr. Dessai SB, E-mail: sampadads@gmail.com

Abstract

PURPOSE: An audit was planned to study the demographics, staging, treatment details, and outcomes of operable endometrial cancers. **METHODOLOGY:** All operable endometrial cancers treated between January 2009 and October 2014 were included in the study. The details regarding demographics, staging, surgical procedure, pathological staging, adjuvant treatment, and outcomes were extracted from the case records. Descriptive statistics was performed. The time-to-event analysis was done by Kaplan–Meier method. Univariate and multivariate analyses were done for disease-free survival (DFS) and overall survival (OS). **RESULTS:** There were 55 patients with a median age of 59 years (35–73 years). The Eastern Cooperative Oncology Group performance status was 1 in 52 patients (94.5%) and 2 in 3 patients (5.5%). Forty-nine patients (89.1%) had disease restricted to endometrium while 6 patients (10.9%) had cervical involvement. The surgery done was Type I hysterectomy in 49 patients (89.1%), Type II in 5 patients (9.1%), and Type III in 1 patient (1.8%). Pelvic lymph node dissection was done in all patients while para-aortic (infrahilar) dissection was done in 48 patients (87.3%). The pathological stages were Stage IA in 19 patients, Stage IB in 15 patients, Stage II in 4 patients, Stage IIIA in 3 patients, Stage IIIB in 2 patients, Stage IIIC1 in 5 patients, Stage IIIC2 in 4 patients, and Stage IV in 3 patients. Grade 1 tumors were seen in 23 patients, Grade 2 in 13 patients, and Grade 3 in 19 patients. The histology was endometrioid in 44 patients, serous in 6 patients, clear cell in 3 patients, and others in 2 patients. Adjuvant treatment was received by 40 patients. With a median follow-up of 2.5 years, the 3-year DFS and OS were 78% and 82%, respectively. Age >59 years, Stage III or greater, and Grade 3 tumors were independent prognostic factors adversely affecting both DFS and OS. **CONCLUSION:** The outcomes in our study are comparable to that seen in Western literature. Elderly status, higher stage, and a poorly differentiated tumor are associated with poor outcomes.

Key Words: Endometrial cancer, India, operable, rural

Introduction

Endometrial cancer is the fourth most common cancer in women worldwide. However, it is the third most common malignancy in Indian women. About 12,335 cases are diagnosed every year and 4773 cases die of this malignancy.[1] The declining incidence of cervical cancer and the predicted rise of endometrial cancer in this century mean that endometrial cancer will be a significant issue in India.[2,3] The traditional management of operable endometrial cancer is by staging laparotomy followed by appropriate adjuvant (as per indication). However, multiple controversies exist in this management.[4] The role of lymphadenectomy, adjuvant radiation, and chemotherapy is not well defined. As a result, variability in the management of endometrial cancer across centers is common. This variability may have an impact on outcomes. However, there is limited literature about the prognosis and practices in the management of endometrial cancer available from India. Lack of such information hampers the development of strategies to improve the outcome and prognosis. This retrospective review was planned to evaluate the outcomes of endometrial cancer patients from rural India.

Methodology

Study setting

This was an Institutional Review Board-approved, retrospective analysis of all endometrial cancer patients who were treated in the time period in between January 2009 and August 2014 at a tertiary cancer care center located in rural Kerala. After surgical staging, all patients were evaluated in multispecialty board discussion for further treatment planning. Patients were classified as low-risk, low-intermediate risk, high-intermediate risk, and high-risk groups according to criteria used in the Postoperative Radiation Therapy in Endometrial Carcinoma trial.[5] These patients were treated in accordance with the National Comprehensive Cancer Network guidelines of respective years.

Data collection

The case numbers were identified from the operation theater records. The case records of these patients were then reviewed and the demographic and clinical details were noted. This included details about diagnosis, staging details, details about outside surgery, details of procedures at our center, postoperative complications, adjuvant treatment, disease status, sites of failure, date of progression, and date of death. The postoperative complications were recorded in accordance with the CTCAE version 4.02.

Data analysis

SPSS 16 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics was performed. The time-to-event analysis was done by Kaplan–Meier method. Disease-free survival (DFS) was calculated from the date

Access this article online

Quick Response Code:

Website: www.indianjcancer.com

DOI: 10.4103/0019-509X.200678

How to cite this article: Dessai S, Adrash D, Geetha M, Arvind S, Bipin J, Nayanar S, *et al.* Pattern of care in operable endometrial cancer treated at a rural-based tertiary care cancer center. Indian J Cancer 2016;53:416-9.

of surgery to the date of first failure. Patients who were disease free were censored at their last follow-up. Overall survival (OS) was calculated from the date of surgery to the date of death. Patients who were alive were censored at their last follow-up. COX regression analysis was performed to identify factors affecting DFS and OS. The factors tested were age (>60 years or 60 years and below), stage (I–II vs. III–IV), Grade (1–2 vs. 3), recipient of adjuvant treatment (yes or no), and Eastern Cooperative Oncology Group performance status (ECOG PS) (0–1 vs. 2).

Results

Demographics

A total of 55 patients were treated at our center from January 2009 to August 2014. Median age was 59 years (35–73 years). Eleven (20%) patients were premenopausal while the rest, i.e., 44 (80%) were postmenopausal. Fifty-two (94.5%) patients had ECOG PS of 1 and the remaining (5.5%) had PS 2. Hypertension was present in 17 (30.9%), diabetes mellitus in 8 (14.5%) and ischemic heart disease in 2 patients (3.6%). Forty-nine patients (89.1%) had clinically disease confined to endometrium while 6 patients (10.9%) had cervical involvement.

Surgical details

All patients were treated with surgery primarily. Forty-nine patients (89.1%) underwent type 1 hysterectomy, 5 patients (9.1%) underwent type 2 hysterectomy, and 1 patient (1.8%) underwent type 3 hysterectomy. Type 2 and/or 3 hysterectomy was done in those 6 (10.9%) patients who had clinical or radiological suspicion of cervical involvement. Bilateral salpingo-oophorectomy was performed in all patients. All patients underwent pelvic lymphadenectomy. Para-aortic lymphadenectomy was performed in 48 (87.3%) patients. The median intraoperative time was 150 min (90–400 min). The median postoperative stay was 6 days (3–22 days).

Adverse events

CTCAE Grade 3–4 surgical morbidity occurred in only 7 (12.7%) patients. Median blood loss was 270 ml (100–1000 ml). Details of intra- and post-operative adverse events are depicted in Table 1. Intraoperative bowel injury occurred in one patient and one patient had ureteric injury which required reimplantation. Metabolic complications (Grade 1–3) occurred in 15 (27.3%) patients. There was no incidence of wound infection.

Histopathological details

Eighty percent of the patients had endometrioid tumors. Clear cell histology was found in 4%, serous in 12%, and carcinosarcoma in 4% of the patients. Twenty-three patients had Grade 1 tumor, 13 had Grade 2 tumor, and 19 had Grade 3 tumor. Tumors were staged according to the FIGO 2009 staging system of endometrial cancers, and the pathological staging is shown in Table 2. There were 19 patients (34.5%) with Stage IA disease, 14 (27.2%) with Stage IB disease, 4 (7.2%) with Stage II disease, 3 (5.4%) with Stage IIIA disease, 2 (3.6%) with Stage IIIB disease, 4 (7.2%) with Stage IIIC1 disease, 5 (9.1%) with Stage IIIC2 disease, 1 (1.8%) with Stage IVA disease, and 2 patients (3.6%) with Stage IVB disease. The histological details with each stage are depicted in Table 2.

Adjuvant treatment details

Details of adjuvant treatment are summarized in Table 2. Adjuvant treatment was received by 38 patients. Thirty-seven patients received adjuvant radiation. External beam radiation (EBRT) and intracavitary brachytherapy (ICBT) were administered in 25 patients, while only ICBT was used in 12 patients. All patients completed radiation schedule. The median EBRT dose was 50.4 Gy (50.4–50.4 Gy). The median equivalent dose for 2 gray for EBRT + ICBT was 58.4 Gy (58–71.4 Gy). The median dose received by only ICBT patients was 7.2 Gy per fraction (6–7.2 Gy), and the median fractions were 3 (3–4). Grade 3–4 toxicity postradiation was seen in 4 patients (10.81%). The three most common acute reactions during radiation were vomiting in 4 patients, diarrhea in 3 patients, and urinary tract infection in 2 patients.

Adjuvant chemotherapy was received by six patients. The chemotherapy regimen was paclitaxel and carboplatin in five patients and ifosfamide-cisplatin in one patient. Ifosfamide and cisplatin were used in patients with mixed mullerian tumor. The median chemotherapy cycles were 6 (1–6 cycles). All except one patient completed adjuvant chemotherapy. This patient had Grade 4 febrile neutropenia

Table 1: Details of intra- and post-operative adverse events

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Intraoperative adverse events					
Ureteric injury	-	-	1	-	-
Bowel injury	-	-	1	-	-
Postoperative adverse events					
Postoperative fever	6	2	-	-	-
Urinary tract infection	-	-	2	-	-
Anemia	20	7	-	-	-
Hypokalemia	9	-	4	-	-
Hyperkalemia	2	1	-	-	-
Hyponatremia	1	-	-	-	-
Lymphocyst	1	-	-	-	-

Events are graded in accordance with the CTCAE version 4.02. The figures depicted are actual patient numbers. Only the highest grade toxicity per patient is depicted in each type of adverse events

Table 2: Details of postoperative management, histopathology, and outcomes according to the stage of the disease

	Stage IA	Stage IB	Stage II	Stage III	Stage IV
Number	19	15	04	14	03
Pathology details					
Type					
Clear	1	-	-	2	-
Serous	1	1	1	3	-
Endometrioid	17	13	3	9	2
MMT	-	1	-	-	1
Grade					
Grade 1	14	3	1	4	1
Grade 2	2	7	-	4	-
Grade 3	3	5	3	6	2
LVSI	1	3	0	4	-
T1 size in cm	3 (1-6)	4 (2-8)	3.5 (1-5)	4.25 (1-10)	4 (1-9)
T2 size in cm	3 (0.5-5)	3 (2-5)	3.5 (1-4)	3.0 (1-10)	4 (1-6)
Adjuvant treatment details					
Adjuvant RT					
EBRT + ICA	3	9	1	12*	-
ICA	5	4	3	-	-
Adjuvant chemotherapy	1 (patient with clear cell histology)	-	-	2 (patients with IIIC2 stage)	3
Outcome details					
DFS					
Median	NR	NR	NR	2.00 years	1.64
3 years (%)	80.7	85.6	66.7	33.8	-
OS					
Median	NR	NR	3.55 years	2.14 years	NR
3 years (%)	100	86.7	66.7	45.9	66.7

*Two patients denied adjuvant treatment. MMT=Mixed Mullerian tumor; LVSI=Lymphovascular space invasion; EBRT=External beam radiation therapy; ICA=Intracavitary; RT=Radiation therapy; DFS=Disease free survival; OS=Overall survival; NR= Not reported

and hence the chemotherapy was stopped. Common acute adverse events seen during chemotherapy were anemia in five patients and vomiting in three patients.

Recurrences

Twelve (21.8%) patients had recurrence. Ten had distant metastasis and two had local recurrence. In the two patients who had local recurrence, one patient had low-risk disease and had not received any adjuvant treatment and could be salvaged with pelvic radiation. The second patient had Stage IB Grade 1 disease and had received vault brachytherapy as adjuvant treatment. She underwent surgical excision as salvage therapy. Of the ten patients who had distant metastasis, they had initial disease with Type II histology in six patients and advanced stage (Stage IIIC and IV) endometrial cancer in four patients. The sites of distant metastasis were lung in four , brain in one, and intra-abdominal disseminated disease in five patients.

Outcomes

The median follow-up was 2.5 years. The median DFS and OS for the whole cohort were not reached. The 3-year DFS and OS were 78% and 82%, respectively [Figure 1]. The DFS and OS of each stage are shown in Table 2. The factors affecting DFS and OS on multivariate analysis are shown in Table 3.

Table 3: Factors affecting disease-free survival and overall survival

Variable	Hazard ratio	95% CI	*P*
DFS			
Elderly age	11.02	1.29–94.40	0.028
Grade 3 status	6.024	1.171–31.25	0.032
Stage III-IV status	5.780	1.189–28.571	0.035
OS			
Elderly age	3.319	0.952–11.577	0.060
Grade 3 status	4.184	1.227–14.286	0.022
Stage III-IV status	6.896	1.761–27.027	0.006

Only factors having a significant *P* value are shown. CI=Confidence interval; DFS=Disease-free survival; OS=Overall survival

Chronic complications

The incidence of lymphedema was Grade 1 in three patients, Grade 2 in three patients, and Grade 3 in three patients. Grade 3 cystitis was seen in one patient. Vaginal stenosis (Grade 2) was seen in two patients. Grade 3 intestinal strictures were seen in two patients. The cumulative incidence of Grade 3–4 chronic complications was 9.1% (five patients).

Discussion

Carcinoma endometrium is the second most common gynecological malignancy at our center. The median

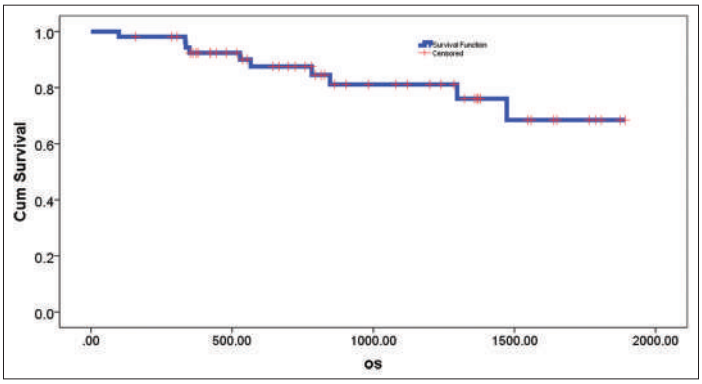

Figure 1: The estimated median overall survival in years

age in our cohort was 59 years. In endometrial cancer series reported from the West, this age is consistently above 60 years while studies reported from India show a median age consistently near 50 years.[6-9] This reflects the differential life expectancy in the state in which the center is located.[10,11] The majority of patients were postmenopausal, one-third had hypertension, and 15% had diabetes mellitus. These factors are consistent with the known risk factors associated with endometrial cancers.[12,13]

The patients selected were operable endometrial cancers. In spite of this selection strategy, only 68.9% had pathological Stage I–II disease. This highlights the importance of surgical treatment in endometrial cancers. In surgical treatment, uterus, fallopian tubes, ovaries, and lymph nodes (pelvic ± para-aortic) are removed. As opposed to this strategy, in radical radiation for endometrial cancer in operable endometrial cancers, radical doses are received by only uterus. This spread of the disease partially explains the inferior results of radical radiation in comparison to surgical treatment.

The surgeries done in our cohort of patients were extensive. Bilateral pelvic lymph node dissections were done in all patients, and para-aortic lymph node dissections were done in 87.5%. These extensive surgeries explain the median intraoperative time of 150 min and a median blood loss of 270 ml. However, cumulative intraoperative adverse event rates of 3.6% attest to the expertise with which these extensive surgeries were performed. The postoperative adverse events were dominated by anemia and metabolic complications, predominantly electrolyte disturbances. There was no incidence of postoperative mortality. This reflects that even in rural setting with surgical expertise and adequate postoperative care, such extensive surgeries can be safely performed.

The recurrence pattern in this study is similar to those reported in other Indian and Western studies.[6,7] Local recurrence was seen in low-risk disease. Such recurrences are salvageable either by radiation or salvage surgery. Distant metastasis as the predominant pattern of recurrence was seen in patients with Type 2 histology or advanced disease. Whether providing chemotherapy in these patients would have prevented distant metastasis is unknown. Studies are ongoing to answer this question. The outcomes (OS) reported in this audit is comparable to the outcome reported in Western and Indian studies.[6,7,14-16] The risk factors associated with OS and DFS, i.e., elderly status, Grade 3 tumors, and advanced disease have been described in other studies too.[6,14]

Conclusion

The outcomes in our study are comparable to that seen in Western literature. Elderly status, higher stage, and a poorly differentiated tumor are associated with poor outcomes.

Acknowledgment

The authors would like to thank all staffs of Malabar Cancer Center.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Globocan 2012 – Home. Available from: http://www.globocan.iarc.fr/Default.aspx. [Last cited on 2015 Aug 19].
2. Nandakumar A, Ramnath T, Chaturvedi M. The magnitude of cancer cervix in India. Indian J Med Res 2009;130:219-21.
3. Evans T, Sany O, Pearmain P, Ganesan R, Blann A, Sundar S. Differential trends in the rising incidence of endometrial cancer by type: Data from a UK population-based registry from 1994 to 2006. Br J Cancer 2011;104:1505-10.
4. SGO Clinical Practice Endometrial Cancer Working Group, Burke WM, Orr J, Leitao M, Salom E, Gehrig P, *et al.* Endometrial cancer: A review and current management strategies: Part II. Gynecol Oncol 2014;134:393-402.
5. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, *et al.* Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. Lancet 2000;355:1404-11.
6. Nout RA, van de Poll-Franse LV, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JW, *et al.* Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol 2011;29:1692-700.
7. Creutzberg CL; PORTEC Study Group. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. Lancet 2010;375:816-23.
8. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, *et al.* Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: Randomized clinical trial. J Natl Cancer Inst 2008;100:1707-16.
9. Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, *et al.* Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer – Results from two randomised studies. Eur J Cancer 2010;46:2422-31.
10. Vijaykumar DK, Anupama R, Gorasia TK, Beegum TR, Gangadharan P. Geriatric oncology: The need for a separate subspecialty. Indian J Med Paediatr Oncol 2012;33:134-6.
11. Patil VM, Chakraborty S, Dessai S, Kumar SS, Ratheesan K, Bindu T, *et al.* Patterns of care in geriatric cancer patients – An audit from a rural based hospital cancer registry in Kerala. Indian J Cancer 2015;52:157-61.
12. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, *et al.* Reproductive, menstrual, and medical risk factors for endometrial cancer: Results from a case-control study. Am J Obstet Gynecol 1992;167:1317-25.
13. MacMahon B. Risk factors for endometrial cancer. Gynecol Oncol 1974;2:122-9.
14. Mahantshetty U, Aggarwal A, Ganesh B, Saoba S, Mulla S, Engineer R, *et al.* Clinical outcome of early-stage endometrioid adenocarcinoma: A tertiary cancer center experience. Int J Gynecol Cancer 2013;23:1446-52.
15. ASTEC/EN, Study Group, Blake P, Swart AM, Orton J, Kitchener H, Whelan T, *et al.* Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): Pooled trial results, systematic review, and meta-analysis. Lancet 2009;373:137-46.
16. ASTEC Study Group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): A randomised study. Lancet 2009;373:125-36.