Archives of Gynecology and Obstetrics (2022) 305:671–681
https://doi.org/10.1007/s00404-021-06187-4

GYNECOLOGIC ONCOLOGY

Survival outcomes of women with grade 3 endometrioid endometrial cancer: the impact of adjuvant treatment strategies

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Received: 4 February 2021 / Accepted: 14 August 2021 / Published online: 27 August 2021

Abstract

Aim This multicenter investigation was performed to evaluate the adjuvant treatment options, prognostic factors, and patterns of recurrence in patients with grade 3 endometrioid endometrial cancer (G3-EEC).

Materials and methods The medical reports of patients undergoing at least total hysterectomy and salpingo-oophorectomy for G3-EEC between 1996 and 2018 at 11 gynecological oncology centers were analyzed. Optimal surgery was defined as removal of all disease except for residual nodules with a maximum diameter ≤ 1 cm, as determined at completion of the primary operation. Adequate systematic lymphadenectomy was defined as the removal of at least 15 pelvic and at least 5 paraaortic LNs.

Results The study population consists of 465 women with G3-EEC. The 5-year disease-free survival (DFS) and overall survival (OS) rates of the entire cohort are 50.3% and 57.6%, respectively. Adequate systematic lymphadenectomy was achieved in 429 (92.2%) patients. Optimal surgery was achieved in 135 (75.0%) patients in advanced stage. Inadequate lymphadenectomy (DFS; HR 3.4, 95% CI 3.0–5.6; $P = 0.016$—OS; HR 3.2, 95% CI 1.6–6.5; $P = 0.019$) was independent prognostic factors for 5-year DFS and OS.

Conclusion Inadequate lymphadenectomy and LVSI were independent prognostic factors for worse DFS and OS in women with stage I–II G3-EEC. Adequate lymphadenectomy and optimal surgery were independent prognostic factors for better DFS and OS in women with stage III–IV G3-EEC.

Keywords Endometrial adenocarcinoma · Grade 3 · Lymphadenectomy

Introduction

Endometrial cancer is the most common neoplasm of the female reproductive system in developed countries, with the highest incidence rates in North America and Europe [1]. Endometrial cancer was traditionally classified as histologically type I and type II (more aggressive) tumors. High-grade histology includes grade 3 endometrioid endometrial cancer (G3-EEC), serous carcinoma, clear cell carcinoma, undifferentiated/dedifferentiated carcinoma, and carcinosarcoma [2]. According to the 2019 recommendations of the International Society of Gynecological Pathologists, endometrioid carcinomas with > 50% solid architecture or with 6–50% solid architecture and diffuse marked nuclear atypia are considered as G3-EEC [2].

G3-EEC has similar phenotypic and molecular features, gene expression profiles, and clinical behavior with those of serous carcinoma, including cases with p53 and p16 overexpression [3–7]. Furthermore, the Cancer Genome Atlas Research Network and recent studies have demonstrated that G3-EEC shares a number of molecular changes (e.g., in PTEN, ARID1A, PIK3CA, and/or KRAS) with type II endometrial cancer [8]. A large prospective study in a population of 5866 endometrial cancer patients indicated that G3-EEC resembled non-endometrioid endometrial cancers, including papillary serous cancer, clear cell cancer, and carcinosarcoma [9].

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Recent studies (PORTEC-3 and GOG-249) demonstrated that multimodal adjuvant treatment (three cycles of chemotherapy plus radiotherapy) did not improve disease-free survival (DFS) or overall survival (OS) rates compared with radiotherapy in patients with grade III or non-endometrioid type early-stage (I–II) endometrial cancer [10, 11]. However, in those two prospective trials, G3-EEC was not analyzed separately given its rarity, and hence optimal adjuvant management of G3-EEC remains controversial. Therefore, the main aim of the present multicenter investigation was to evaluate the adjuvant treatment options, prognostic factors, and patterns of recurrence in patients with G3-EEC.

Materials and methods

The medical records of women who underwent total hysterectomy and salpingo-oophorectomy for G3-EEC between January 1996 and December 2018 at 11 gynecological oncology centers were analyzed. All patients provided informed consent at admission regarding the use of their medical information for research purposes. The clinical data consisted of medical, surgical, pathological, and demographic characteristics, serum cancer antigen 125 levels, date and type of surgery, omentectomy, adequate systematic lymphadenectomy, residual tumor tissue after surgery, myometrial invasion (MI), lymphovascular space invasion (LVSI), numbers of excised and positive lymph nodes (LNs), type of adjuvant therapy, date of any recurrence, recurrence pattern, date of the last medical examination, and date of death.

All pathological specimens from the primary surgery were examined and interpreted by expert gynecological pathologists from the participating institutions who had experience with gynecological malignancies. All tumors were staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system [12]. In patients treated before 2009, stage was determined retrospectively based on surgical and pathological assessments.

The adjuvant treatment policies were decided by the attending physician or the multidisciplinary tumor board at each participating institution. Hence, the adjuvant treatment modalities were not standardized throughout the study period. The adjuvant treatment type (i.e., only external beam radiotherapy (EBRT) and/or vaginal brachytherapy (VBT), only chemotherapy (CT), EBRT + CT, VBT + CT, or EBRT + VBT + CT, was applied according to the institutional practices at the time of diagnosis. Patient follow-up was performed according to the clinical guidelines. Survival was censored on December 31, 2018. The survival status of the patients was recorded as alive or dead at the time of the last follow-up.

Adequate pelvic lymphadenectomy was defined as the removal of at least 15 pelvic LNs, and adequate para-aortic lymphadenectomy was defined as the removal of at least 5 para-aortic LNs [13, 14]. Adequate systematic lymphadenectomy was defined as the removal of at least 15 pelvic and at least 5 paraaortic LNs. Optimal surgery was defined as removal of all disease except for residual nodules with a maximum diameter ≤ 1 cm, as determined at completion of the primary operation. Suboptimal surgery was defined as residual disease with a tumor diameter > 1 cm. Locoregional recurrence was defined as recurrence distal to the pelvic inlet (true pelvis), abdominal recurrence was defined as recurrence between the pelvic inlet and the diaphragm, and extra-abdominal recurrence was defined as all other types of recurrence. Ascites and peritoneal carcinomatosis were considered as abdominal recurrence.

DFS was defined as the time from the date of primary surgery to the detection of recurrence or the last follow-up, and OS as the time from the date of primary surgery to death or the last follow-up. Survival was analyzed using the Kaplan–Meier method, and the results were compared using the log-rank test. Logistic regression analysis was conducted to identify the factors predicting survival. Unpaired data were compared using the χ^2 test or Student's t test. All statistical analyses were performed using MedCalc software (ver. 16.0 for Windows; MedCalc Software, Mariakerke, Belgium). In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 493 G3-EEC patients were identified for the study. 28 cases with missing medical records were excluded from the study. Therefore, our study was conducted with retrospective file records of 465 women with G3-EEC. The demographic data and pathological characteristics of the patients, and the recurrence and survival rates of the patients are presented in Table 1. The median age of the patients at the time of diagnosis was 59 (29–86) years. The median postoperative follow-up time for all patients was 41 months (range 1–240 months). The 5-year DFS and OS rates in the entire cohort were 50.3% and 57.6%, respectively.

The treatment modalities of the patients are shown in Table 2. All patients underwent total hysterectomy and salpingo-oophorectomy. Adequate systematic lymphadenectomy was achieved in 429 (92.2%) patients. Omentectomy was performed in 424 (91.2%) patients. Optimal surgery was achieved in 135 (75.0%) patients in advanced stage. A total of 429 (92.2%) patients received adjuvant therapies, including chemotherapy in 11 (2.4%), chemoradiotherapy in 265 (57.0%), and adjuvant radiotherapy in 153 (32.9%).

Table 1 Clinical features of patients with grade III endometrial adenocancer (G3-EAC)

	G3EC ($n=465$)
Age, years; median (min–max)	59 (29–86)
Age ≥ 60 years; *n* (%)	225 (48.8)
Parity; mean ± SD	3.3 ± 2.2
Postmenopause; *n* (%)	400 (86.0)
Abdominal acid; *n* (%)	9 (1.9)
Elevated CA125 (> 35 U/ml); *n* (%)	91 (19.5)
Ascites; *n* (%)	9 (1.9)
Size of tumor ≥ 2 cm; *n* (%)	348 (74.8)
Depth of myometrial invasion (≥ 1/2); *n* (%)	333 (70.9)
Cervical invasion; *n* (%)	71 (15.2)
Lymphovascular space invasion; *n* (%)	218 (46.8)
Lymphadenectomy; *n* (%)	
No	21 (4.5)
Pelvic lymphadenectomy	10 (2.1)
Pelvic-paraaortic lymphadenectomy	434 (93.3)
Pelvic LN count; mean (min–max)	29.2 (16–67)
Para-aortic LN count; mean (min–max)	22.1 (6–51)
Stage (FİGO), *n* (%)	
IA	234 (50.3)
IB	17 (3.7)
II	34 (7.3)
IIIA	23 (4.9)
IIIB	17 (3.7)
IIIC	97 (20.9)
IV	43 (9.2)
5 year DFS rate (%)	50.3
5 year OS rate (%)	57.6
DFS, month; median (min–max)	38.1 (1–240)
OS, month; median (min–max)	41.1 (1–240)
Early stage (FIGO I–II)	
5 year DFS rate (%)	72.3
5 year OS rate (%)	76.4
Advance stage (FIGO III–IV)	
5 year DFS rate (%)	26.7
5 year OS rate (%)	38.9

Table 2 Treatment protocols of patients grade III endometrial adenocancer (G3-EAC)

	G3EC ($n=465$)
Adequate lymphadenectomy; *n* (%)	
Yes	429 (92.2)
No	36 (7.7)
Type of surgery in advanced stage	
Optimal	135 (75.0)
Suboptimal	45 (25.0)
Omentectomy; *n* (%)	
Yes	424 (91.2)
No	41 (8.7)
Therapy; *n* (%)	
Only surgery	36 (7.7)
Surgery + Adj. radiotherapy	153 (32.9)
Surgery + Adj. chemotherapy	11 (2.4)
Surgery + Adj. chemoradiotherapy	265 (57.0)
Adjuvant radiotherapy alone (*n* 153)	
VBT	101 (66.0)
EBRT	43 (28.1)
EBRT + VBT	9 (5.8)
Adjuvant chemotherapy alone (*n* 11)	
Paclitaxel + Carboplatin	8 (72.7)
Adriamycin + Cisplatin	2 (18.1)
Cisplatin	1 (9.1)
Adjuvant chemoradiotherapy (*n* 265)	
Paclitaxel + Carboplatin + VBT	40 (15.0)
Paclitaxel + Carboplatin + EBRT	28 (10.5)
Paclitaxel + Carboplatin + VBT + EBRT	42 (15.8)
Ifosfamide + Mesna + Adriamycin + VBT	30 (11.3)
Ifosfamide + Mesna + Adriamycin + EBRT	10 (3.7)
Ifosfamide + Mesna + Adriamycin + VBT + EBRT	67 (25.2)
Ifosfamide + Mesna + Etoposid + EBRT	6 (2.2)
Adriamycin + Cisplatin + EBRT + VBT	21 (7.9)
Cisplatin + EBRT + VBT	21 (7.9)

The most frequently used chemotherapy regimen was paclitaxel and carboplatin (118/276 patients, 42.7%), followed by ifosfamide, mesna, and adriamycin (107/276 patients, 38.7%) (Table 2).

Disease recurrence occurred in 102 patients (21.9%). There were 42 (41.2%) loco-regional recurrences and 22 (21.6%) extra-abdominal failures. The recurrence rate was 27.5% (28/102) in early-stage and 72.5% (74/102 patients) in advanced-stage ($P<0.001$). Most of the patients (74/102, 72.5%) with recurrence were managed with CT with/without secondary debulking surgery. Twelve (11.8%) patients were managed with secondary debulking surgery only. In patients with recurrent G3-EEC, the median OS was 26.7 (1–144) months and the median DFS 20.2 (1–112) months (Table 3).

The results of univariate and multivariate analyses of predictors of DFS and OS are shown in Table 4. Cox multivariate analysis showed that inadequate lymphadenectomy (HR 3.4, 95% CI 3.0–5.6; $P=0.016$) was independent prognostic factors for 5-year DFS. Similarly, inadequate lymphadenectomy (HR 3.4, 95% CI 1.7–6.5; $P=0.016$) was independent prognostic factors for 5-year OS. According to Kaplan–Meier analysis, survival curves of insufficient lymphadenectomy, early stage and optimal surgery, which showed significant effects on DFS and OS according to Cox regression analysis, are shown in Fig. 1.

In subgroup analyses according to the FIGO stage, age ≥ 60 years (HR 2.6, 95% CI 1.2–5.6; $P=0.009$),

Table 3 Clinical and treatment features of recurrent patients with grade III endometrial adenocancer (G3-EAC)

Reoccurrence	$N=102$
Reoccurrence location; *n* (%)	
Locoregional	42 (41.2)
Abdominal	38 (37.3)
Widespread	22 (21.6)
Stage of recurrent patient; *n* (%)	
Early Stage (I–II)	28 (27.5)
Advance Stage (III–IV)	74 (72.5)
Recurrent treatment protocol; *n* (locoregional, abdominal, widespread)	
Only Surgery	12 (10,2,0)
Only Chemotherapy	54 (20,30,4)
Surgery + chemotherapy	20 (12,0,8)
Only Radiotherapy	3 (0,0,3)
Surgery + radiotherapy	5 (0,5,0)
Chemoradiotherapy	3 (0,1,2)
Surgery + chemotherapy	5 (0,0,5)
DFS, month; median (min–max)	20.2 (1–112)
Locoregional	26.3 (8–112)
Abdominal	21.1 (4–96)
Widespread	11.3 (1–42)
OS, month; median (min–max)	26.7 (1–144)
Locoregional	32.2 (10–144)
Abdominal	26.9 (6–112)
Widespread	17.2 (1–48)

presence of LVSI (HR 3.1, 95% CI 1.8–7.2; $P=0.007$), and inadequate lymphadenectomy (HR 3.2, 95% CI 2.0–5.4; $P=0.013$) were independent prognostic factors for decreased 5-year DFS in women with FIGO stage I–II G3-EEC. The same clinicopathological factors, age ≥ 60 years (HR 3.2, 95% CI 0.9–8.9; $P=0.008$), presence of LVSI (HR 3.0, 95% CI 1.6–5.8; $P=0.002$), and inadequate lymphadenectomy (HR 3.1, 95% CI 2.0–5.6; $P=0.026$), were also independent prognostic factors for decreased 5-year OS (Table 5). In patients with FIGO stage III–IV G3-EEC, adjuvant radiotherapy (with or without chemotherapy), adequate lymphadenectomy, and optimal surgery were significant independent prognostic factors for better 5-year DFS and OS rates (Table 6).

Discussion

Conducting prospective trials in patients with G3-EEC is difficult because of the rarity of the disease. This multicenter retrospective study was performed to investigate the current clinical status of this rare tumor and to explore the possibilities for future prospective clinical trials. To our knowledge, this is the largest retrospective study of the survival outcomes of women with G3-EEC. Our findings suggest that adequate lymphadenectomy seem to be independent prognostic factors for better DFS and OS rates in women with G3-EEC.

Although the incidence of grade 3 tumors among EECs has increased over the last several years (from 18% in 2006 to 32% in 2014) [15], there is no standard treatment for G3-EEC. Few studies have been conducted in large numbers of patients with G3-EEC [15, 16]. Adjuvant therapy appears to be important given the aggressive nature of the disease and mounting evidence regarding the benefits of adjuvant therapy.

Previous studies of G3-EEC reported incidences of early-stage and advanced-stage disease of 54–82% and 18–46%, respectively; similar to our cohort (61% for early-stage and 39% for advanced-stage) [6, 16–21]. Lymphadenectomy and optimal surgery were performed in 87–95% [20] and 94% [6] of patients, respectively; in the present study, the corresponding figures were 92% and 95%, respectively. The recurrence rate in previous studies has been reported to range between 12 and 25% [18, 22–25]. These discrepancies in results were probably due to differences in the proportions of patients at different disease stages. Similarly, we found the recurrence rates as 9.8% and 41.1% in women with early- and advanced-stage disease, respectively. Previous studies have reported a wide range of 5-year DFS (45–77%) and OS (51.3–81.7%) rates, possibly due to heterogeneous study populations (i.e., patients with different stages of disease) [6, 19–21]. The survival results presented here may be useful for future studies as the current study was performed with a large number of G3-EEC patients with both early- and advanced-stage disease. The 5-year DFS and OS rates were 72.3% and 76.4%, respectively, in patients with FIGO stage I–II disease and 26.7% and 38.9%, respectively, in patients with FIGO stage III–IV disease in the present study.

The defined prognostic factors for type I endometrioid endometrial cancer is generally accepted for patients with G3-EEC. However, it is very important to investigate the effects of prognostic factors on survival in large numbers of patients with early- or advanced-stage G3-EEC. Nonetheless, previous studies have yielded conflicting results. A previous study showed that MI affects DFS and OS [18, 26], while other studies showed that MI had no effect on OS [16, 19]. Similarly, the effect of adjuvant therapy on survival outcomes is controversial [24, 27]. Stage, LN metastasis, vaginal involvement, and adnexal involvement have been shown to affect OS [16, 19]. However, only adequate lymphadenectomy was defined as independent prognostic factors for increased 5-year DFS and OS rates in women with G3-EEC in the current study. We also performed subgroup analyses to investigate prognostic factors affecting survival outcomes

Table 4 Results of univariate and multivariate analyses of the disease-free and overall survival of patients with grade III endometrial adenocancer (G3-EAC)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Disease-free survival						
Age (≥ 60 years)	2.1	1.1–3.1	0.205	1.8	0.9–3.4	0.123
Adjuvant therapy (none)	2.1	1.5–2.8	0.062	1.8	1.2–2.6	0.094
Applied						
Radiotherapy	–	–	–	–	–	–
Chemotherapy	1.1	1.0–1.2	0.345	1.2	1.1–1.4	0.102
RT + CT	1.1	0.9–1.4	0.541	1.6	1.0–2.3	0.203
İnadequate lymphadenectomy	3.4	3.0–5.6	0.016	3.2	2.1–4.2	0.021
Omentectomy	0.8	0.6–0.9	0.136	0.9	0.6–1.3	0.221
Depth of myometrial invasion (≥ 1/2)	1.3	1.1–1.4	0.158	1.3	1.1–1.5	0.408
Endocervical glandular involvement	1.6	1.4–1.8	0.109	1.6	1.2–2.2	0.212
LVSI	2.2	1.8–2.5	0.091	2.3	1.9–2.9	0.081
Tumor size (> 2 cm)	1.8	1.2–2.5	0.126	1.4	1.2–1.6	0.702
Optimal Surgery	0.3	0.1–0.9	0.021	0.4	0.1–0.8	0.025
Early stage (I–II)	0.2	0.1–0.5	0.003	0.3	0.1–0.4	0.008
Overall survival						
Age (≥ 60 years)	1.9	0.6–4.8	0.070	1.6	1.1–2.1	0.247
Adjuvant therapy (none)	2.1	1.7–3.2	0.103	2.0	1.0–3.9	0.210
Applied						
Radiotherapy	–	–	–	–	–	–
Chemotherapy	1.4	1.0–1.8	0.414	1.1	1.0–1.3	0.246
RT + CT	1.2	101–1.4	0.238	1.0	0.8–1.2	0.351
İnadequate lymphadenectomy	3.3	2.6–6.2	0.028	3.4	1.7–6.5	0.016
Omentectomy	0.7	0.5–0.8	0.098	0.8	0.7–1.0	0.106
Depth of myometrial invasion (≥ 1/2)	1.9	0.9–4.6	0.365	2.3	1.6–3.8	0.088
Endocervical glandular involvement	1.4	0.8–2.5	0.198	1.2	0.5–3.5	0.601
LVSI	1.9	1.5–2.5	0.071	2.1	1.2–4.1	0.121
Tumor size (> 2 cm)	1.6	1.1–2.3	0.203	1.5	1.2–2.1	0.267
Optimal Surgery	0.3	0.1–0.7	0.011	0.4	0.2–0.7	0.021
Early stage (I–II)	0.2	0.1–0.5	0.003	0.3	0.1–0.5	0.005

in women with early- versus advanced-stage G3-EEC. As expected, optimal surgery and adequate lymphadenectomy were indicative of improved survival outcomes. Additionally, the presence of LVSI and age ≥ 60 years were factors predicting decreased DFS and OS rates in patients with early-stage disease according to the Cox regression analyses. However, in advanced-stage tumors, we were unable to find out any prognostic factors for DFS or OS other than optimal surgery, adequate lymphadenectomy and adjuvant radiotherapy.

Although all surgical procedures were performed by experienced gynecologic oncologists, we used a uniform definition for adequate pelvic and para-aortic lymphadenectomy to limit bias in the lymphadenectomy results. In this large cohort, lymphadenectomy was related to improved DFS and OS rates in both early- and advanced-stage patients, specifically for those in whom more than 15 pelvic nodes and 5 para-aortic nodes were removed. Although LN involvement is absent in early-stage disease, the increased survival of early-stage patients was likely due to greater exploration and closure of the metastasis pathway. The therapeutic value of removing normal-appearing, normal-sized LNs has been disputed, but removal of such LNs does provide the most accurate staging to optimize the postoperative treatment modality. In addition, as ASTEC [28] did not provide guidelines for management of high-risk endometrial cancer, and given the results of SEPAL [29], comprehensive staging using pelvic and para-aortic lymphadenectomy is still recommended. Until the results of the GOG 249 trial (phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial carcinoma) become available, these approaches are still standard, and additional procedures such as peritoneal washings, omentectomy, and peritoneal biopsy are still incorporated at the surgeon's

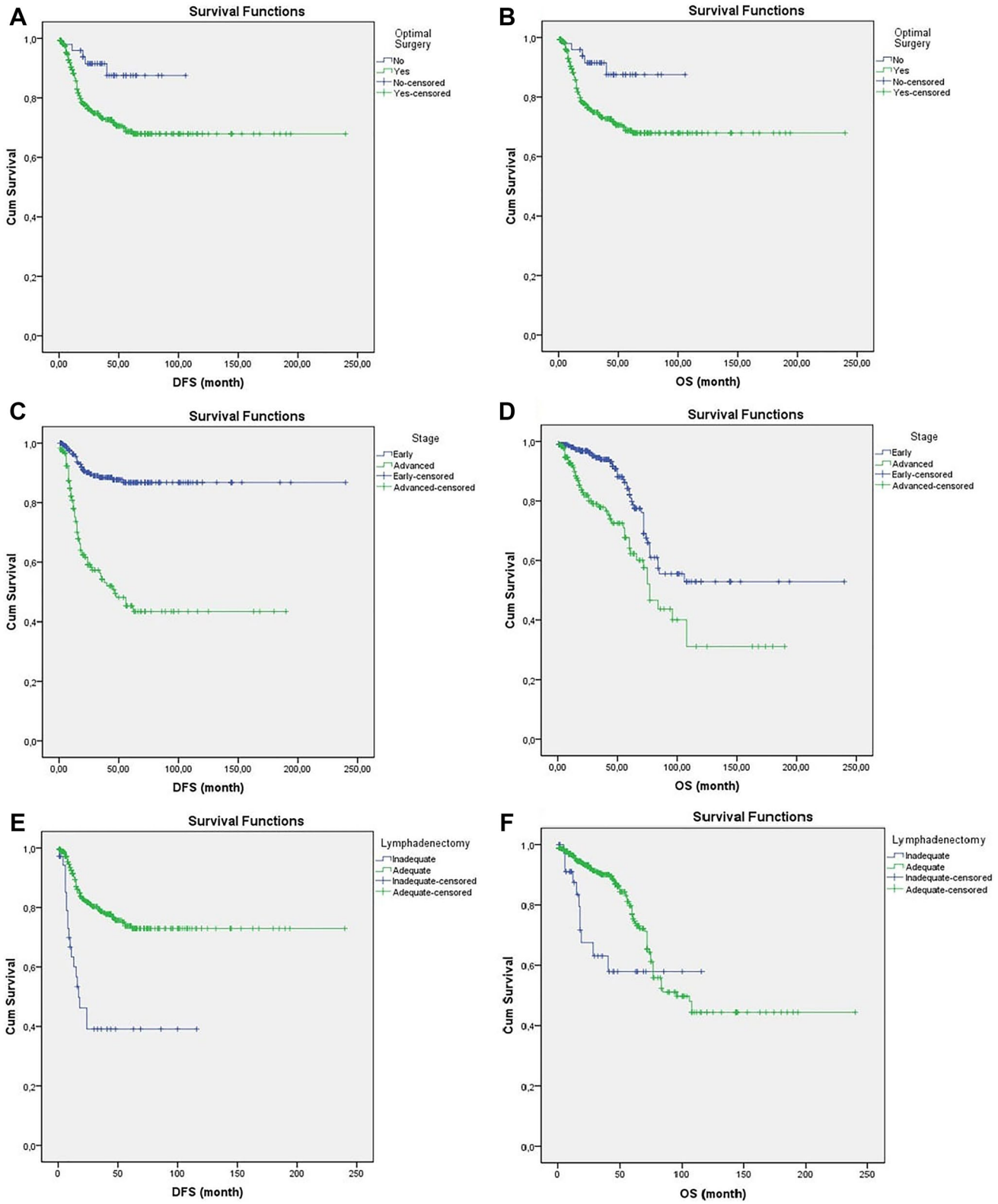

Fig. 1 Disease-free survival curves according to optimal surgery ($P=0.012$) (**A**), early stage ($P=0.001$) (**C**), adequate lymphadenectomy ($P=0.001$) (**E**). Overall survival curves according to optimal surgery ($P=0.012$) (**B**), early stage ($P=0.001$) (**D**), adequate lymphadenectomy ($P=0.016$) (**F**)

Table 5 Results of univariate and multivariate analyses of the disease-free and overall survival of patients with early stage grade III endometrial adenocancer (G3-EAC)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Disease-free survival						
Age (≥ 60 years)	2.6	1.2–5.6	0.009	2.5	0.8–8.9	0.011
Adjuvant therapy (none)	1.7	1.0–2.8	0.424	1.3	0.6–2.9	0.342
Applied						
Radiotherapy	–	–	–	–	–	–
Chemotherapy	0.8	0.7–0.9	0.855	0.9	0.7–1.0	0.380
RT + CT	1.8	1.1–3.9	0.274	2.2	1.1–4.6	0.096
Inadequate lymphadenectoy	3.2	2.0–5.4	0.013	2.8	1.5–5.6	0.031
Omentectomy	0.8	0.6–1.1	0.302	0.9	0.8–1.0	0.104
Depth of myometrial invasion (≥ 1/2)	1.1	0.8–1.4	0.402	1.2	1.1–1.6	0.754
Endocervical glandular involvement	1.3	0.9–1.9	0.140	1.2	1.0–1.5	0.521
LVSI	3.1	1.8–7.2	0.007	3.2	1.6–5.2	0.006
Tumor size (> 2 cm)	1.9	1.1–3.7	0.061	1.7	1.5–2.1	0.070
Overall survival						
Age (≥ 60 years)	3.2	0.9–8.9	0.008	2.8	1.2–6.3	0.023
Adjuvant therapy (none)	1.8	1.2–2.6	0.819	1.5	0.5–4.8	0.137
Applied						
Radiotherapy	–	–	–	–	–	–
Chemotherapy	1.1	0.6–2.0	0.151	1.0	0.8–1.2	0.360
RT + CT	1.4	0.6–3.1	0.092	0.7	0.3–1.4	0.091
Inadequate lymphadenectomy	3.1	2.0–5.6	0.026	3.0	2.0–4.6	0.018
Omentectomy	0.9	0.6–1.5	0.098	1.0	0.8–1.3	0.468
Depth of myometrial invasion (≥ 1/2)	1.6	0.9–2.5	0.267	3.0	1.3–7.0	0.821
Endocervical glandular involvement	1.8	1.2–2.8	0.104	1.7	1.2–2.4	0.145
LVSI	3.0	1.6–5.8	0.002	2.9	1.5–6.2	0.005
Tumor size (> 2 cm)	1.9	1.6–2.6	0.068	1.5	1.2–1.9	0.722

discretion due to lack of convincing evidence discouraging use of these methods.

The primary motivation for evaluating the outcomes of G3-EEC stems from the need to refine strategies for adjuvant management. The poor survival of these patients highlights the need for improved adjuvant therapeutic strategies. The guidelines of the European Society for Medical Oncology/European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology (ESMO/ESGO/ESTRO) and the National Comprehensive Cancer Network recommend VBT for patients with G3-EEC with MI < 50% [19, 30–32]. However, in patients with stage IA G3-EEC and risk factors such as LVSI, adjuvant therapy consisting of EBRT is controversial according to ESMO/ESGO/ESTRO guidelines [30]. Both guidelines recommend that patients with stage IB–II G3-EEC to undergo EBRT [19, 30, 32]. The type of systemic therapy used is decided according to additional risk factors. Recently, larger multicenter studies (PORTEC-3 and GOG-249) demonstrated that adjuvant chemoradiotherapy (three cycles of chemotherapy plus radiotherapy) improved neither PFS nor OS compared to radiotherapy in high-risk endometrial cancer patients. Adjuvant radiotherapy alone remains an effective and appropriate adjuvant treatment for high-risk endometrial cancer [10, 11]. Consistent with the literature, our regression analyses according to the FIGO stage suggested that adjuvant therapy did not affect DFS or OS in patients with early-stage disease. In contrast, adjuvant radiotherapy (with or without chemotherapy) was an independent prognostic factor for DFS and OS in patients with advanced-stage G3-EEC. Adjuvant radiotherapy after optimal surgery appears to be important for the treatment of patients with advanced-stage G3-EEC according to our findings.

The main limitations of this study were the retrospective nature of the study, the absence of a central pathology review, and the absence of uniform standards to guide decision-making and patient selection in terms of adjuvant treatment modalities. In addition, some changes in adjuvant treatment modalities occurred over the long study period. Differences in adjuvant treatment modalities may have affected the validity of results. Finally, as the patients in our study were treated in 11 gynecological cancer centers, interpretation of the data was also restricted due to differences in

Table 6 Results of univariate and multivariate analyses of the disease-free and overall survival of patients with advanced stage grade III endometrial adenocancer (G3-EAC)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Disease-free survival						
Age (≥ 60 years)	1.6	1.1–2.3	0.406	1.3	0.9–1.7	0.408
Adjuvant therapy (none)	3.1	1.9–5.6	0.002	3.0	2.1–4.4	0.035
Applied						
Radiotherapy	–	–	–	–	–	–
Chemotherapy	1.4	1.1–1.6	0.457	1.3	1.0–1.5	0.277
RT + CT	1.2	0.8–1.8	0.653	1.2	1.1–1.3	0.296
Inadequate lymphadenectomy	3.0	1.1–8.8	0.039	2.8	1.8–5.9	0.041
Omentectomy	0.6	0.4–0.9	0.056	0.7	0.3–1.3	0.094
Depth of myometrial invasion (≥ 1/2)	1.6	1.3–1.9	0.288	1.5	1.4–1.6	0.511
Endocervical glandular involvement	2.0	1.5–2.4	0.089	1.9	1.3–2.6	0.147
LVSI	1.8	1.4–2.1	0.103	1.7	1.1–2.5	0.703
Tumor size (> 2 cm)	1.7	1.2–2.4	0.296	1.3	0.9–1.7	0.436
Optimal surgery	0.3	0.2–0.4	0.002	0.4	0.3–0.6	0.009
Overall survival						
Age (≥ 60 years)	1.3	1.0–1.5	0.321	1.2	1.0–1.7	0.109
Adjuvant therapy (none)	3.3	1.6–5.9	0.009	3.2	1.5–7.4	0.012
Applied						
Radiotherapy	–	–	–	–	–	–
Chemotherapy	1.5	1.2–1.9	0.744	1.3	1.0–1.6	0.402
RT + CT	1.3	1.1–1.6	0.508	1.1	0.9–1.3	0.654
Inadequate lymphadenectomy	2.9	1.0–9.1	0.026	2.7	1.1–6.9	0.022
Omentectomy	0.7	0.6–0.9	0.105	0.8	0.5–1.2	0.086
Depth of myometrial invasion (≥ 1/2)	2.1	0.8–5.6	0.966	2.0	1.5–2,6	0.967
Endocervical glandular involvement	1.2	0.5–2.8	0.658	1.0	0.5–2.7	0.845
LVSI	1.6	0.9–2.7	0.092	1.5	0.8–2.4	0.167
Tumor size (> 2 cm)	1.5	1.2–2.1	0.176	1.6	1.4–1.9	0.362
Optimal surgery	0.4	0.2–0.8	0.015	0.5	0.4–0.7	0.026

institutional practices. Therefore, we may not have presented the clinical results of relapse patients in an objective and uniform manner, as relapse treatment is not uniform and depends on institutional practices. However, our findings add to the limited knowledge of G3-EEC therapy.

The relatively large number of patients included, similar demographic characteristics, availability of long-term follow-up data, and performance of surgeries by qualified gynecologic oncologists were the strengths of the current study. All of these factors increased the effectiveness of the results and reduced the limitations of the cohort.

In conclusion, our findings suggest that in women with early-stage G3-EEC, inadequate lymphadenectomy, LVSI status, and age are significant prognostic factors affecting DFS and OS. Adjuvant therapy modalities had no effect on DFS or OS in early-stage patients. The results of the present study also indicated that optimal surgery, inadequate lymphadenectomy, and adjuvant radiotherapy are independent prognostic factors in women with advanced-stage G3-EEC. Based on these findings, comprehensive surgical staging and optimal cytoreductive surgery with adjuvant radiotherapy is the cornerstone of treatment for advanced-stage G3-EEC patients. Larger prospective studies in similar patient populations are required to verify the findings of the present study.

Author contributions Concept: KG, VG, MZM, JS, OA. Design: KG, VG, MMM, JS. Data Collection or processing: VG, JS, MM, AM, AO, HS, TS, NY, TT, TO, ST, AA, JM, NB. Analysis or interpretation: KG, VG, MM. Literature search: KG, VG, MM, GB, AO, HS, TS, NY, TT, TO, MAV. Writing: KG, MM, VG.

Funding None.

Declarations

Conflict of interest All of author declare that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent No informed consent was obtained in the retrospective file scan.

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