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Survival analyses of patients with non-endometrioid endometrial carcinoma

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Abstract

Non-endometrioid endometrial carcinoma seems to be less common with a poor prognosis. Due to the lack of standard treatment options and worse survival rates of non-endometrioid endometrial carcinoma, we aimed to investigate these patients inclusively. In total, 492 women with endometrial cancer who were treated in a gynecologic oncology center were examined. Patients with a final histopathologic diagnosis of non-endometrioid endometrial carcinoma were evaluated in respect of demographic characteristics, prognostic aspects, and survival outcomes. We identified 94 patients with the histopathologic results of non-endometrioid endometrial carcinoma. The performance of the systematic lymphadenectomy and adjuvant treatment rate were 96.9% and 92.6%, respectively. Recurrence of the disease was detected in 32 (34%) women and disease-related mortality occurred in 28 (29.8%) women. Multivariate Cox proportional regression analyses determined tumor size, adnexal involvement, and lymphovascular space invasion as independent predictors of overall survival. Larger tumor size, adnexal, and lymphovascular space invasion are important factors in determining prognosis in non-endometrioid endometrial carcinoma patients according to our findings. Besides, high rates of surgical staging and adjuvant chemotherapy and radiation therapy may contribute to improved survival outcomes; in addition to having potential advantages of providing prognostic information. Therefore, a multidisciplinary therapeutic approach should be planned from the early stages for all patients in this group. Nevertheless, comprehensive prospective studies are necessary to optimize the treatment strategies and support successful treatment modalities.

Keywords: Comprehensive staging, endometrial carcinoma, non-endometrioid carcinoma, survival

Introduction

Endometrial carcinoma (EC) is the most frequent malignancy of the female genital tract [1]. Although the vast majority of the patients are diagnosed with endometrioid histopathology at an early stage with better outcomes, non-endometrioid histopathology is responsible for 10-15% of all endometrial cancers, with an unfavorable prognosis. Non-endometrioid endometrial carcinoma (NEEC) is distinct from endometrioid carcinomas in terms of patients' characteristics, clinic features, and management [2] and is the cause of more than 45% of all the EC deaths [3].

Subtypes of non-endometrioid endometrial carcinoma, such as clear cell, serous, carcinosarcoma, and mixed types, are believed to have aggressive potential rather than endometrioid EC. Staging surgery is commonly recommended in the treatment strategies of those patients with high-risk histologic subtypes [4-6].

Various prognostic factors, that were found to be related to poor prognosis, have been explicated for NEEC [7-9]. On the other hand, a limited number of studies on this subject have been able to reveal significant results regarding the association between clinicopathologic factors and prognosis [7-11]. As a result of inadequate standard treatment choices and worse survival rates of NEEC, it is necessary to define the patients' characteristics and analyze clinical outcomes efficiently. Consequently, we analyzed prognostic factors for survival in the NEEC patients.

Material and Methods

In total, 492 women with endometrial cancer who were treated

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in a gynecologic oncology center were examined between February 2012 and May 2020. Patients with final histopathological diagnosis of undifferentiated, serous, clear, mixed, mucinous, and dedifferentiated endometrial carcinoma, and carcinosarcoma were a part of the study. Patients with endometrioid carcinoma and who had endometrial and ovarian carcinoma simultaneously, whose surgeries were performed in a different center, or who did not continue their follow-up regularly were excluded from the study. Informed consent was obtained from all the patients.

Demographic parameters such as age, presence of menopause, body mass index, co-morbidities, and the ASA score were gathered. Also, preoperative serum CA 125 values and clinical features of the patients with NEEC were collected. Data including reports of the surgical procedures, follow-up, and the pathological findings were reviewed. Based on histopathologic reports; histologic type, depth of myometrial invasion, tumor size, grade, cervical stromal invasion, omental metastasis, adnexal involvement, lymphovascular space invasion, number of lymph nodes removed, and lymph node metastasis were documented. Follow-up duration and recurrence, disease-related mortality, and overall survival were examined. Neoadjuvant and adjuvant treatment rates, type of adjuvant therapy (chemotherapy, radiotherapy, combined therapy, or Sandwich therapy), and patient compliance were recorded. After the performance of surgery, all patients had been followed 4 times a year for the first 2 years, then a follow-up schedule was designed twice a year for 3 years, and annual follow-up examinations were performed in the later years.

Surgical staging was the first step in the treatment of patients with NEEC. All patients with NEEC underwent hysterectomy and bilateral salpingo-oophorectomy, peritoneal cytology, pelvic-paraaortic lymphadenectomy, and omentectomy regardless of uterine findings [12]. The staging was accomplished according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines [13]. The decision on adjuvant treatment was given by the multi-disciplinary team and adjuvant therapy consisted of radiation therapy, chemotherapy, or combined therapy [14].

Approval of the study was obtained from the Institutional Review Board (Project number KA 20/311, approval date 11 August 2020).

Statistical analyses

SPSS 21.0 software program was used for the statistical analyses (SPSS Inc. Chicago, USA). Shapiro-Wilk test was applied to check the normality for continuous variables. Numerical data are assessed as median values (minimum-maximum) or mean values with standard deviation when needed. The Chi-square test was practiced for analyzing the categorical variables between the groups.

Overall survival time was explained as the time from the date of operation to the time of death or the date of the last follow-up. Disease-free survival (DFS) was described as the time after treatment during which no sign of cancer is detected. To estimate survival analyses Kaplan-Meier survival curves were generated from the SPSS software. A Cox regression model with stepwise selection was performed to determine variables. The adjusted treatment effect for these selected variables was measured. A p-value <0.05 was determined statistically significant.

Results

A total of 94 women with non-endometrioid endometrial carcinoma, which constitutes 19.1% of all endometrial cancer cases, were enrolled in the study. Eight patients (7.8%) who did not carry on their follow-ups were excluded from the study. The baseline data of the non-endometrioid endometrium carcinoma patients are presented in Table 1.

Table 1. Baseline data of the non-endometrioid endometrium carcinoma patients

Age at diagnosis (years), median (range)	64(31-83)
Premenopausal/Postmenopausal (n)	17/79
BMI (kg/m²), median (range)	31.5(19.2-68)
ASA score, n (%)	
ASA II	37(38.5%)
ASA III	59(61.5%)
Comorbidity conditions, n (%)	
Hypertension	37(38.5)
Diabetes mellitus	28(29.2)
Smoking	11(11.5)
Preoperative CA125 level (IU/L), median (range)	21(5-1064)

Table 2. Disease characteristics of the non-endometrioid endometrial carcinoma patients

Histology, n (%)	
Serous	50(53.2)
Carcinosarcoma	30(32)
Others (clear (n=8), mucinous (n=1), undifferentiated (n=3), neuroendocrine (n=1), unclassified (n=1))	14(14.8)
Serous / non-serous histologic type (n)	50/44
Stage, n (%)	
Stage I	44(46.8)
Stage II	5(5.3)
Stage III	34(36.2)
Stage IV	11(11.7)
Number of lymph nodes removed, median (range)	61(13-136)
Number of pelvic lymph nodes	33(12-83)
Number of paraaortic lymph nodes	28(7-74)
Adjuvant therapy, n (%)	87(92.6)
Chemotherapy	30(34.5)
Radiotherapy	8(8.5)
Combined therapy	46(57)
* The sandwich (preradiotherapy- chemotherapy- radiotherapy) therapy	*16(18.4)

Laparotomy was used in 76 patients and laparoscopy was used in 18 patients as surgical procedures. In 93 patients (96.9%), systematic lymphadenectomy and omentectomy were accomplished. Lymphadenectomy was not achieved in 3 patients, since the origin of the tumor in 2 patients could not be evaluated by the pathologist during the operation and 1 patient was hemodynamically intolerant due to bleeding. The disease characteristics of the non-endometrioid endometrial carcinoma patients are summarized in Table 2. All cases had grade 3 tumors, except one case with grade 2 mucinous tumor.

Neoadjuvant therapy was administered in 5 (5.2%) patients and adjuvant therapy was applied in 87 (92.6%) patients. Adjuvant therapy compliance was 82.8% (72/87), while the reasons for patients not to maintain the adjuvant chemotherapy were mostly due to the intolerance of the complications. The median overall

survival and disease-free survival were 27.5 months and 20 months. Recurrence of cancer was detected in 32 (34%) women and disease-related mortality had occurred in 28 (29.8%) women. Loco-regional recurrence occurred in 10 (10.6%) patients: 4 of these recurrences were in the lymphatic region and 6 of them were in the vaginal cuff or pelvic region. Distant organ metastasis, including multiple (n=13), intraabdominal (n=6), lung (n=2) and brain (n=1) metastasis, occurred in 22 (23.4%) patients.

Table 3 demonstrates the effects of the prognostic parameters on survival in non-endometrioid endometrial carcinoma patients. There is no statistical significance between groups including age, BMI, tumor size, and omental involvement. However, prognostic parameters such as CA 125 level, myometrial invasion, cervical stromal and adnexal invasion, pelvic-paraaortic lymph node metastasis, lymphovascular space invasion (LVSI), and stage were identified to be significantly higher in deceased patients.

The 5-year overall survival (OS) period was found to be 64.5% for the entire group with the Kaplan Meier log-rank test. Kaplan-Meier survival analyses for prognostic parameters in non-endometrioid endometrial carcinoma patients are presented in Figure 1 (a, b). CA 125 level, myometrial invasion, cervical stromal and adnexal involvement, omental involvement, lymphovascular space invasion (LVSI), and pelvic-paraaortic lymph node metastasis affected survival in log-rank analyses., while large tumor size, elder age, and obesity did not affect survival according to survival analyses (p>0.05). Additionally, tumor size (Hazards Ratio (HR) 1.17, 95% CI:1.02-1.30, p=0.009), adnexal involvement (HR 4.99, 95% CI:1.97-12.7, p=0.001) and lymphovascular space invasion (HR 4.6, 95% CI:1.01-21.04, p=0.049) were found to be independent parameters of overall survival in NEEC patients by multivariate Cox regression analyses (Table 4).

Table 3. The effects of the prognostic parameters on survival in patients with non-endometrioid endometrial carcinoma

		Non-aliven (%)	Aliven (%)	Pvalue, Oddsratio, value (CI)
Age, years	≤65(n=68)	17(60.7)	49(74.2)	0.14*
	>65(n=28)	11(39.3)	17(25.8)	
BMI (kg/m²)	<30(n=32)	7(29.2)	24(46.2)	0.13*
	≥30(n=46)	17(70.8)	28(53.8)	
CA125level (IU/L)	<35(n=56)	13(48.1)	41(70.7)	0.044*
	≥35(n=31)	14(51.9)	17(29.3)	OR=2.6(1.0-6.7CI)
Tumorsize (cm)	<2(n=9)	1(4)	8(15.1)	0.15*
	≥2(n=69)	24(96)	45(84.9)	
Myometrial invasion (%)	<50(n=52)	9(34.6)	41(68.3)	0.004
	≥50(n=36)	17(65.4)	19(31.7)	*OR=4.1(1.6-10.8CI)
Cervical stromal invasion	(-)(n=69)	15(53.6)	52(88.1)	<0.001
	(+)(n=20)	13(46.4)	7(11.9)	*OR=6.5(2.2-19.7CI)
Adnexal involvement	(-)(n=64)	13(46.4)	49(81.7)	0.001
	(+)(n=26)	15(53.6)	11(18.3)	*OR=5.1(1.9-13.9CI)
Omentum involvement	(-)(n=77)	20(74.1)	56(88.9)	0.07*
	(+)(n=14)	7(25.9)	7(11.1)	
Lymphovascular space invasion	(-)(n=30)	3(12)	25(45.5)	0.003
	(+)(n=52)	22(88)	30(54.5)	*OR=6.1(1.7-22.8CI)
Pelvic lymph node metastasis	(-)(n=68)	13(48.1)	53(82.8)	0.001
	(+)(n=25)	14(51.9)	11(17.2)	*OR=5.2(1.9-14.1CI)
Paraaortic lymph node metastasis	(-)(n=69)	15(55.6)	52(81.3)	0.02
	(+)(n=24)	12(44.4)	12(18.7)	*OR=3.5(1.3-9.3CI)

*Chi-Square test was used for statistical analyses

Table 4. Cox regression analyses of different prognostic parameters in patients with non-endometrioid endometrial carcinoma

	B	P-value	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Step 1					
Tumor size (mm)-continuous	0.1	0.09	1.13	0.98	1.30
High CA 125 level	0.4	0.52	1.48	0.45	4.92
Deep myometrial invasion	0.5	0.38	1.61	0.55	4.67
Cervical stromal invasion (+)	0.3	0.60	1.38	0.42	4.51
Adnexal involvement (+)	1.3	0.05	3.56	1.01	12.5
Omentum involvement (+)	-0.3	0.98	0.98	0.23	5.45
Lymphovascular space invasion (+)	1.6	0.06	5.06	0.92	27.85
Pelvic lymph node metastasis (+)	0.5	0.39	1.74	0.49	6.12
Paraaortic lymph node metastasis (+)	-1.2	0.87	0.89	0.20	3.84
Step 7					
Tumor size (mm)	0.2	0.009	1.17	1.02	1.30
Adnexal involvement (+)	1.6	0.001	4.99	1.97	12.70
Lymphovascular space invasion (+)	1.5	0.049	4.60	1.01	21.04

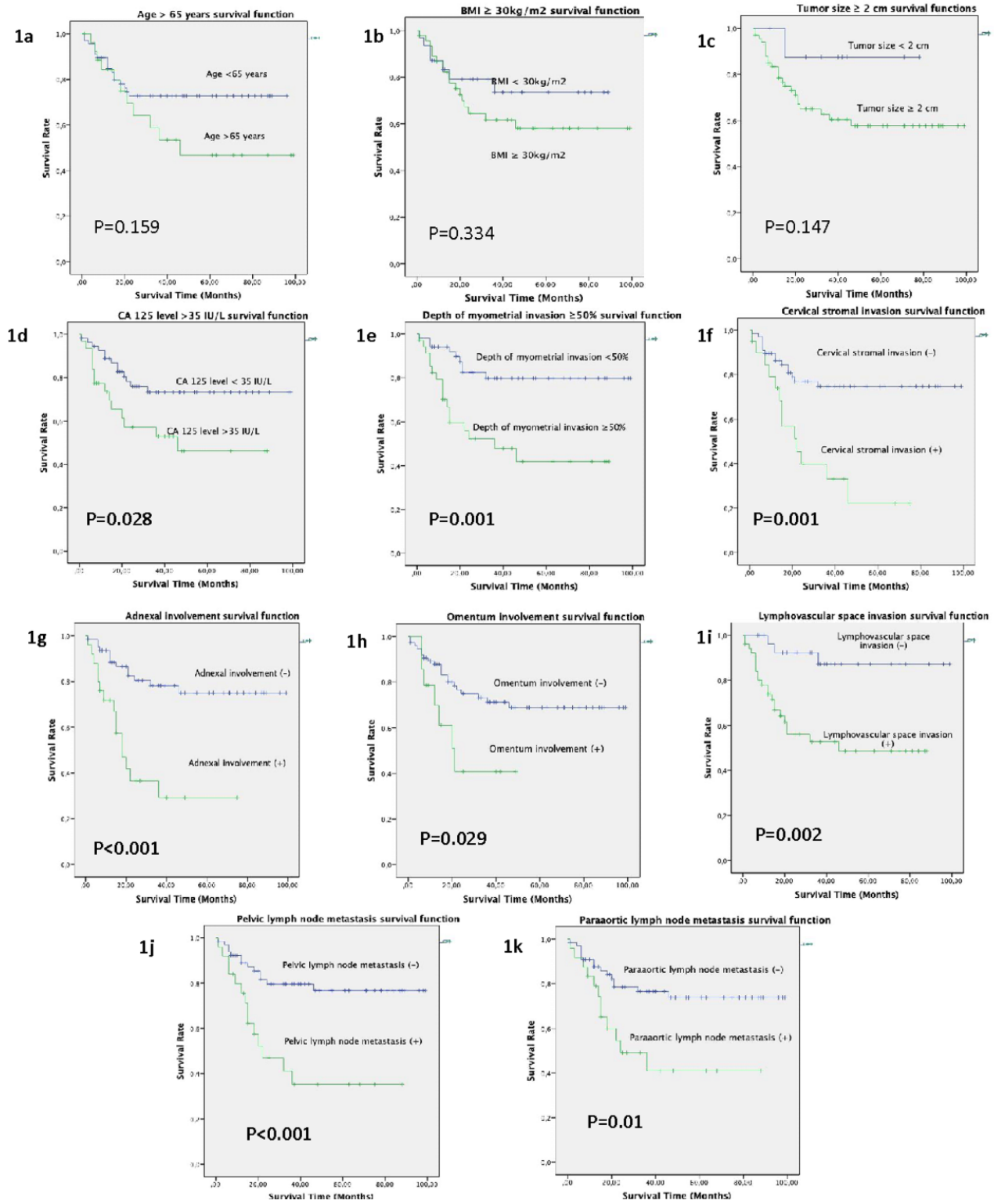

Figure 1. Kaplan-Meier survival analyses for prognostic parameters in non-endometrioid endometrial carcinoma patients
The estimated mean survival time for all the parameters was presented as shown below:
1a= Age ≤65 years 72.2±4.9 months, Age>65 years 58±8.8 months, p=0.159
1b= BMI<30 kg/m2 68.4±6.8 months, BMI ≥30 kg/m² 63.9±6.6 months, p=0.334
1c= Tumor size<2cm 70.1±7.4 months, Tumor size ≥2cm 63.9±5.6 months, p=0.147
1d= CA 125 level ≤35 IU/L 75.9±5.5 months, CA 125 level >35 IU/L 49.8±7.3 months, p=0.028
1e=Depth of myometrial invasion<50% 81.6±5.3 months, Depth of myometrial invasion ≥50% 47±7 months, p=0.001
1f=Cervical stromal invasion (-) 76.6±5 months, Cervical stromal invasion (+) 32±6.4 months, p=0.001
1g=Adnexal involvement (-) 78.3±5 months, Adnexal involvement (+) 32.2±6.4 months, p<0.001
1h=Omentum involvement (-) 73.2±4.9 months, Omentum involvement (+) 27.8±5.3 months, p=0.029
1i=Lymphovascular space invasion (-) 88.5±5.7 months, Lymphovascular space invasion (+) 50.5±5.8 months, p=0.002
1j=Pelvic lymph node metastasis (-) 79.3±4.8 months, Pelvic lymph node metastasis (+) 41.6±7.7 months, p<0.001
1k=Paraaortic lymph node metastasis (-) 76.8±5 months, Paraaortic lymph node metastasis 45.8±8.2 months, p=0.01

Discussion

Nonendometrioid histologic type of endometrial carcinoma, which has a relatively rare incidence, has also a poor prognosis when compared with the endometrioid histologic type of EC. In the study, serous adenocarcinoma (53.2%) and carcinosarcoma (32%) were the most frequent histologic types of NEEC. Based on our experience and study results, the rate of neoadjuvant therapy, the performance of systematic lymphadenectomy, adjuvant treatment, recurrence, and disease-related mortality was 5.2%, 96.9%, 92.6%, 34%, and 29.8% in patients with NEEC, respectively. Also, tumor size, adnexal, and lymphovascular space invasion were described as independent predictors of overall survival in NEEC patients.

Rates of non-endometrioid subtypes of EC have been increasing in a concerning trend [15]. Also, the incidence of NEEC in our cohort was 19.1%. Increasing weight gain, aging, and decreased usage of hormone replacement therapy may affect these trends [16]. Based on our study results, 5-year overall survival was 64.5 months. The 2018 registries from The Surveillance, Epidemiology and End Results (SEER) showed that the 5-year survival rate was actually lower in NEEC patients (57.5%) in the U.S. Our higher survival rate may be related to the high performance of adjuvant therapy. The vast majority of the NEEC patients (92.6%) were treated with adjuvant therapy in our cohort. Also, in previous studies, the disease-specific survival advantage of adjuvant chemoradiotherapy was most prominent in women with NEEC [17]. However, the function of adjuvant chemotherapy in NEEC patients should be inspected in ongoing and future trials.

NEEC patients who comprise %10-20 of the endometrial carcinoma, experienced the highest rates of lymph node metastasis [18,19]. We performed systematic lymphadenectomy with a high rate (96.9%) in patients with NEEC and 25.5% of the patients had lymph node metastasis. Our center is a tertiary gynecologic oncology unit with a high volume and provides a substantial rate of surgical staging. Only in three patients, lymphadenectomy was not performed due to hemodynamic intolerance and uncertainty of histologic type of cancer. According to the study of Venigella et al., lymphadenectomy was independently related to decreasing the risk of mortality in NEEC patients. For all non-endometrioid histologies, pelvic lymphadenectomy was reported to be superior to not performing lymphadenectomy, while the survival benefit of additional paraaortic lymphadenectomy was solely demonstrated for patients with the histologic type of serous carcinoma [19]. Though, other studies denoted that, the natural history of NEEC would not be changed by systematic pelvic lymphadenectomy, which may only provide prognostic information and guide for further adjuvant treatment [20,21]. Also, recent literature showed that comprehensive lymphadenectomy did not provide better survival results in early-stage uterine serous carcinoma patients [22]. Based on our study, the occurrence of lymph node metastasis was an important prognostic factor that supported the prognostic function of staging by performing systematic lymphadenectomy.

All the cases were high grades in our study. High-grade tumors behave similarly in all endometrial cancers, regardless of whether they are endometrioid or non-endometrioid and a big deal of the patients present with distant metastasis even in the early stage of the disease [10,23]. However, in those studies, the type of the tumor and restricted population size may affect the results. The aggressive phenotype of NEEC is notorious, with the majority of patients being high grade, so this issue should be evaluated with large comprehensive studies.

According to our study, all the prognostic parameters including CA 125, myometrial invasion, cervical stromal and adnexal invasion, omental involvement, pelvic-paraaortic lymph node metastasis, and lymphovascular space invasion were important for the survival of the NEEC patients. Therefore comprehensive staging surgery should be performed, in addition to hysterectomy, bilateral salpingo-oophorectomy, systematic lymphadenectomy, and omentectomy in NEEC patients [24-26]. Although each clinicopathologic factor had an effect on survival according to Kaplan Meier analyses, Cox regression analyses showed that the most important parameters, which included LVSI, adnexal involvement, and tumor size, were related to higher mortality rates. Coherent with the literature, the study demonstrated that elevated preoperative serum CA 125 level was an independent risk factor for survival. Also, high CA 125 is associated with extrauterine involvement and disseminated disease [27-29].

The rate of laparoscopic surgery was 19.2% in our cohort. According to National Cancer Database, the minimally invasive surgery was performed in 32.2-57.6% with an increasing trend in NEEC patients (n=13.392) [30]. After further studies with large populations, demonstrating its safety with no adverse effect on survival, this procedure will be a reasonable approach in patients with NEEC.

Our study has inherent limitations including its retrospective design, presence of possible confounders, and involving single-center experience. Also, the limited number of subgroups of NEEC did not allow analyses among subgroups. On the other hand, similar comprehensive staging and treatment to all cohorts, and the histology being confirmed by a dedicated gynecologic pathologist are the strengths of the study.

Conclusion

In conclusion, comprehensive surgical staging and adjuvant therapy may contribute to better survival outcomes in non-endometrioid endometrial carcinoma patients. Also, tumor size, adnexal, and lymphovascular space invasion (p=0.049) are independent predictors of overall survival in these patients. Therefore, multidisciplinary therapeutic approach should be planned from the early stages for all patients in this group. Future prospective multi-centric studies are needed to determine accurate prognostic parameters, which affect survival, and to tailor the optimal treatment strategies.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

Approval of the study was obtained from the Institutional Review Board (Project number KA 20/311, approval date 11 August 2020).

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