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Original Article

Histopathological features of endometrial cancer. A cross sectional study

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Abstract: Background: Endometrial cancer, as one of the most common gynecological cancers, lacks a comprehensive understanding of its survival parameters. The present study aims to analyze the effect of histopathological and clinical factors on the likelihood of recurrences. Methods: This cross-sectional study was conducted from 2015 to 2021 on endometrial cancer patients at a university-affiliated medical center. Demographic, histopathological data, and molecular markers were collected. Data were compared between patients with or without recurrences or mortality. Results: After analyzing data from 180 cases, it was revealed that 16 cases (8.9%) experienced mortality following the recognition of recurrences. Endometrioid type was the most prevalent in non-surviving patients (75%) (P=0.01). The frequency of patients who survived was higher in the age group of 45-60 years (P=0.01). The highest mortality occurred in patients with high-grade endometrial cancer at stage 2, larger tumor sizes, and lymphovascular involvement at the time of the initial diagnosis. Comorbidities such as diabetes, cardiac diseases, or having more than two comorbidities were also associated with higher mortality (P=0.018). Additionally, 37.5% of cases with mortality had lymph node involvement compared to 7.1% in the opposite group (P<0.001). Conclusion: The mortality rate of Asian endometrial cancer patients was 8.9%, with higher mortality observed in older patients, clear cell and serous papillary pathology, and patients with lymphovascular involvement or larger tumors.

Keywords: Endometrial cancer, mortality, recurrences

Introduction

Endometrial cancer is a significant public health concern, particularly in light of its increasing prevalence among younger populations. Several studies have investigated prognostic factors in endometrial cancer, shedding light on the impact of lifestyle changes, nutritional factors, and environmental patterns on its incidence [1]. Globally, endometrial cancer has been on the rise, with an age-standardized incidence of 8.2% in 2018 [2, 3]. In Iran, a country facing the burden of non-communicable diseases, endometrial cancer has been responsible for a notable 3.5 cases per 100,000 females in 2020, underscoring the urgency of understanding clinicopathological factors that influence prognosis in this region [4].

Prior research has emphasized the importance of histopathological factors in predicting prognosis, highlighting the role of factors such as extrauterine proliferation and lymphatic metastasis [5, 6]. However, there remains a lack of knowledge about these prognostic factors in Iran, including epidemiological and histopathological information, which prompted us to undertake this four-year survival study on endometrial cancer cases.

Understanding the histopathology of endometrial cancer is crucial for predicting prognosis and tailoring treatment approaches. This cancer exhibits various histological subtypes, with endometrioid carcinoma being the most prevalent, accounting for approximately 93.9% of cases in our study population [8]. Other subtypes, such as clear cell carcinoma (2.8%) and papillary serous cancer (3.3%), present distinct histopathological characteristics and clinical behaviors [8].

Histopathological factors play a pivotal role in determining the extent of extrauterine proliferation, lymphatic metastasis, and, ultimately, patient prognosis [7, 8]. These factors, coupled

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with patients' clinical characteristics, guide treatment decisions and impact outcomes. Given the substantial economic burden of cancer, particularly in resource-limited settings, a deeper understanding of the histopathological intricacies of endometrial cancer can inform personalized treatment strategies and optimize healthcare resource allocation.

Endometrial carcinoma presents various histological features, predominantly characterized by distinct subtypes like endometrioid carcinoma, clear cell carcinoma, and papillary serous carcinoma, each exhibiting unique architectural and cellular patterns [2]. Histological grade, ranging from well-differentiated (Grade 1) to poorly differentiated (Grade 3), also plays a crucial role in defining the cancer's characteristics [3]. To investigate the association between these pathological features and patient survival, the study likely employed statistical analyses, such as Kaplan-Meier survival curves and regression models, to assess how the specific histological subtypes and grades correlate with overall survival and disease-free survival rates. These analyses would help determine whether certain histological features serve as prognostic indicators for endometrial carcinoma, influencing patient outcomes [5].

To contextualize our study within the existing research landscape, it is essential to discuss previous studies that have explored prognostic factors in endometrial cancer. Additionally, we must clarify the unique contribution of our research, which lies in its focus on the Iranian population and its potential to inform individualized and precise decision-making regarding limited healthcare resources, including adjuvant treatment and surveillance modalities. By addressing these points, we can better demonstrate the significance and innovation of our study within the broader field of endometrial cancer research.

Methods and material

Study design

This is a prospective cross-sectional study that was performed in 2015-2021 in an educational hospital affiliated to Isfahan University of Medical Science, Iran. The current study was conducted on all patients with endometrial cancer referring to the medical centers using census sampling method and The Ethics Committee of Isfahan University of Medical Sciences approved this study (IR.MUI.MED.REC.1398.699).

Inclusion and exclusion criteria

We included all patients diagnosed with endometrial cancer of any histologic type and grade based on histopathology reports. Informed consent for participation and data publication was obtained from all included patients, and those who did not provide consent were excluded.

Data gathering

After recruiting the patients, the demographic data (age, weight, number of pregnancies, history of smoking, history of oral contraceptive usage, and medical history), the initial and last histopathologic findings based on initial endometrial sampling and the final pathologic reports after hysterectomy were recorded. The patients were followed after the definite surgical intervention in the order of total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without lymph node dissection based on patients underlying comorbidities or intraoperation findings. In cases of incomplete data on patient surveillances and survival, the documents were completed using phone calls or other social media tools or the patient were excluded in case of no way of contacting or missing the follow-up. Based on surgical finding and after multidisciplinary team consulting patients with high or high-intermediated risk factors were candidate for adjuvant treatment in the type of external or internal radiotherapy and/or chemotherapy based on the last consensus on endometrial cancer management by NCCN (national comprehensive cancer network), and then the patients were followed again based on these consensus guidelines with every 3-6 months of examination and cervical cytology and also yearly and/or symptom-based computerized chest and abdomino-pelvic tomography according to our institutional protocols till September 2021 and all findings were documented.

Observational indicators

In this study on endometrial cancer, the observational indicators encompass a wide range of factors. We also compared demographic and tumor data based on survival type. Survival

rates, both overall and 4-year disease-free survival, are evaluated using Kaplan-Meier analysis. Prognostic factors, including age, tumor characteristics, and comorbidities, are assessed for their impact on outcomes. Recurrence patterns, follow-up data, and the utility of cervical Pap smears in diagnosis are also explored. These indicators collectively contribute to a comprehensive understanding of endometrial cancer in the study population, shedding light on patient profiles, treatment outcomes, and key factors influencing prognosis.

Statistical analysis

The acquired data were inputted into the Statistical Package for Social Sciences (SPSS) version 24. Quantitative data were expressed as mean ± standard deviation, while qualitative data were presented as frequency distributions (percentages). Data analyses involved the use of independent t-tests and Chi-square tests. A significance threshold of *P*-value <0.05 was applied. Additionally, survival analyses were conducted using the Kaplan-Meier method and the Life Table method to assess both disease-free survival and overall survival rates.

Results

Study population

In this study, a total of 207 patients diagnosed with endometrial cancer were initially enrolled. However, during the initial stage, 27 of these patients were excluded from the analysis due to either patient requests or missed surveillance visits. Consequently, the study's final population included 180 cases. These participants had an average age of 57.8 years (±9.7), and their mean body mass index (BMI) was 30.39 kg/m^2. It was noteworthy that a significant portion of the patients, 148 out of 180 (82.2%), had a history of at least one pre-existing medical condition, and approximately half of the participants, specifically 50.6%, had two or more concurrent diseases. Among these medical conditions, diabetes mellitus was the most prevalent, affecting 57.2% of all study participants.

Pre-operative cervical pap-smear

The pre-operative cervical pap-smear reports revealed limited cases with abnormal findings. Specifically, there were two cases with ASC-H (atypical squamous cells-cannot exclude high-grade lesion) and HSIL (high-grade squamous intraepithelial lesion), both of which were subsequently diagnosed with endometrioid carcinoma in stage 3. Additionally, two cases exhibited ASC-US (atypical squamous cells-undetermined significance) in the pre-operative cervical pap-smear results, and these cases were associated with early-stage endometrial carcinoma.

Histology of tumors

Among the 180 cases included in the study, the most common histological type was endometrioid carcinoma, accounting for 169 cases (93.9% of the total). Clear cell carcinoma was observed in 5 cases (2.8%), while papillary serous cancer was identified in 6 cases (3.3%). In addition to the standard total hysterectomy and bilateral salpingo-oophorectomy procedures, pelvic ± para-aortic lymphadenectomy was performed in 154 patients. Among these patients, micro-metastases were detected in only 16 cases. Notably, among these 16 cases with micro-metastases, 3 cases had evident uterine-confined disease as indicated pre-operatively.

Further relationships

Post-operative treatment was considered for 43 cases among the 160 patients in stage 1, based on their risk category. The correlation between post-operative treatment and overall and 4-year disease-free survival is presented in **Table 1**. Given the substantial number of cases in the early stage (160 cases), the majority of the analysis was focused on patients with stage 1 endometrial cancer to ensure more robust and validated results. An apparent relationship was observed between mortality, age, and tumor size, which was found to be significant in stage 1a. However, no significant differences were found with regard to BMI, past medical history, oral contraceptive pill (OCP) usage, adjuvant treatment, the number of dissected lymph nodes, or serial screening pap-smear (**Table 2**). Factors that had a significant effect on overall survival (OS) included patient age, type of tumor, stage and grade of tumor, comorbidities, tumor size, positive lymphovascular space invasion (LVSI), and microscopically positive lymph nodes for malignancy. Another

Table 1. Endometrial cancer patient detailed data based on based on post-operative pathology-risk category in correlation with mortality and recurrences

Risk category	Each category explanation	Number of cases	Mortality	Recurrence's rate
High-risk	Serous papillary in pathology	6	2	5
	Clear cell in pathology	5	2	4
	Stage 1b/Grade 3	3	1	1
	Stage 3/4	20	7	9
	Stage 2	2	1	1
High-intermediate	<70 years old	8	1	2
	>70 years old	2	0	1
	LVI	4	1	3
	Grade 2/3	8	1	2
	Stage 1b	10	1	3
Low-risk	Stage 1a	121	3	8
	Stage 1b	20	2	3
	LVI	1	0	0
	Cytology positive	1	0	1
	With PLND	120	5	11
	Without PLND	21	0	0

Table 2. The correlation between number of dissected lymph node and prognosis in stage 1 of endometrial cancer cases

Variable		Mortality	N	Mean	Std. Deviation	*p*-value
Stage 1a	Number of patients with dissected lymph-node	Live	123	5.9024	4.19683	0.569
		Dead	4	8.2500	5.96518	
	Number of patient with histologically positive lymph node	Live	102	0.0000	0.00000[b]	1.000
		Dead	4	0.0000	0.00000[b]	
Stage 1b	Number of patient with dissected lymph-node	Live	28	6.6429	3.40168	0.361
		Dead	4	8.2500	1.50000	
	Number of patient with histologically positive lymph node	Live	26	0.0000	0.00000[b]	1.000
		Dead	4	0.0000	0.00000[b]	

S: stage, G: grade. b. It cannot be computed because the standard deviations of both groups are 0.

noteworthy point in predicting patient survival across all stages was the significant correlation between the presence of lymphovascular invasion and the likelihood of detecting micrometastases in dissected lymph nodes. Based on our data, the majority of patients who survived had endometrioid type tumors (93.3%), followed by papillary serous and concomitant endometrioid tumors of the uterus and ovary (2.4% each), and clear cell carcinoma (1.8%). Regarding age, the frequency of patients who survived was higher in the age group of 45-60 years (P=0.010). In general, as age increased, the mortality rate also increased. Further supplementary data are shown in **Tables 3**-**7**.

Follow-up data

The estimated median follow-up, determined using the inverse Kaplan-Meier method, was 51.32 months for both disease-free survival and overall survival. Overall survival was calculated over a 4-year period due to the absence of cases in the fifth year of follow-up. The 4-year overall survival rates were 85% for all patients and 96% for patients in stage 1, as depicted in **Figure 1**. Additionally, the overall 4-year free survival rate was 78% for all patients, with a higher rate of 83% observed in cases with stage 1 disease. According to our data, the probability of mortality in early-stage disease

Table 3. Analysis of demographic and tumor related variables

Variable		Abundance	Percent
Age	30-45	20	11.1
	45-60	78	43.3
	60-80	82	45.6
Age (mean±SD)		57.84±9.69	
Education	Illiterate	35	19.4
	Elementary - Cycle	85	47.2
	Diploma - Above Diploma	52	28.9
	Bachelor's degree and higher	8	4.4
Gravidity	0	10	5.6
	1-2	49	27.2
	3-5	102	56.7
	6 and above	19	10.6
BMI	<21	1	0.6
	21-24	5	2.8
	24-30	99	55
	30-40	66	36.7
	>40	9	5
Tumor type	Endometrioid	16	91.7
	Clear cell	5	2.8
	Papillary serosa	6	3.3
	Simultaneous endometriosis of the uterus and ovaries	4	2.2
Comorbidities	Diabetes multiuse	103	57.2
	Hypertension	96	53.3
	Heart disease	16	8.9
	Hyperlipidemia	43	23.9
	Hypothyroidism	12	6.7
	≥2 underlying disease	91	50.6
	Smoking	0	0
Consumption of OCP	Yes	33	18.3
	No	147	81.7
Resistance area	Urban life	115	63.9
	Rural life	65	36.1

BMI: body mass index, S: stage, G: grade.

was 1% in the first year, gradually increasing to 4% at the end of the 4-year follow-up period.

Discussion

While the United States has experienced a considerable number of deaths among newly diagnosed cases, with approximately 11,350 deaths out of 63,230 new cases, our study in the Iranian population revealed a mortality rate of 8.5%, primarily among patients with advanced stages and older age [7, 8]. In our present study, we observed a 4-year survival rate of 91% in early-stage patients and 85% across all stages. Our investigation highlighted the significant impact of FIGO stage, histopathological type, the presence of comorbidities, and patient age as prognostic factors, consistent with previous research findings [3, 9]. Furthermore, a study conducted by Medenwald and colleagues in 2020, involving 12,718 patients over 17 years, explored the effects of radiotherapy in addition to surgery. Their findings indicated that higher stages and grades were associated with increased mortality rates [10]. In a 2008 study in Japan by Takeshima, which involved 63 endometrial cancer cases, a mortality rate of 10.2% was reported, with

Table 4. The surgical stage, grade, and the frequency of recurrences or non-survived cases in all endometrial cases

Variable		Frequency	%	Recurrence number (*p*-value: <0.001)	Mortality (*p*-value: <0.001)
Grading	S1A.G1	113	62.8	4	1
	S1A.G2	9	5.0	4	2
	S1A.G3	6	3.3	4	1
	S1B.G1	19	10.6	4	2
	S1B.G2	10	5.6	4	1
	S1B.G3	3	1.7	1	1
	S2.G3	2	1.1	1	1
	S3.G1	5	2.8	2	1
	S3.G2	5	2.8	3	2
	S3.G3	7	3.9	3	3
	S4.G2	1	0.6	1	1
	Total	180	100.0	31	16

Table 5. Demographic comparison based on survival

Variable	Survival	Number	Mean	*p*-value
Age	Live	152	56.94	0.01
	Dead	8	67.12	
BMI	Live	152	30.06	0.107
	Dead	8	33.12	
Size of tumor (mm)	Live	152	2.03±1.21	<0.001
	Dead	8	3.75±0.59	

Table 6. Comorbidity comparison based on survival

Variable	Survival		Total (N=160)	*p*-value
	Live	Dead		
Diabetes mellitus	85 (0.56%)	6 (75%)	91 (57%)	0.288
Hypertension	78 (51%)	4 (50%)	82 (51.25%)	0.942
Heart Disease	10 (7%)	1 (0.13%)	11 (6.9%)	0.442
Hyperlipidemia	119 (78%)	6 (75%)	125 (78.1%)	0.826
Thyroid disease	12 (8%)	0	12 (7.5%)	>0.99
Variant comorbidities	72 (47%)	5.00 (63%)	77 (48.2%)	0.404
Presence of at least one underling disease	123 (81%)	8 (100%)	131 (81.9%)	0.172

Table 7. Evaluation the frequency of recurrences site in endometrial cancer cases

Variable		Frequency	Total population percent	Recurrence percentage
Recurrence location	Vaginal cuff	16	8.9	51.6
	Lung	2	1.1	6.45
	Lung + intestine	3	1.7	9.67
	Lung + vaginal cuff	4	2.2	12.9
	Intestine	1	0.6	30.22
	Left inguinal	1	0.6	30.22
	Lung + liver	4	2.2	12.9
Total vaginal cuff ± other		20	11.11	64.51
Total lung ± other		13	7.22	41.93

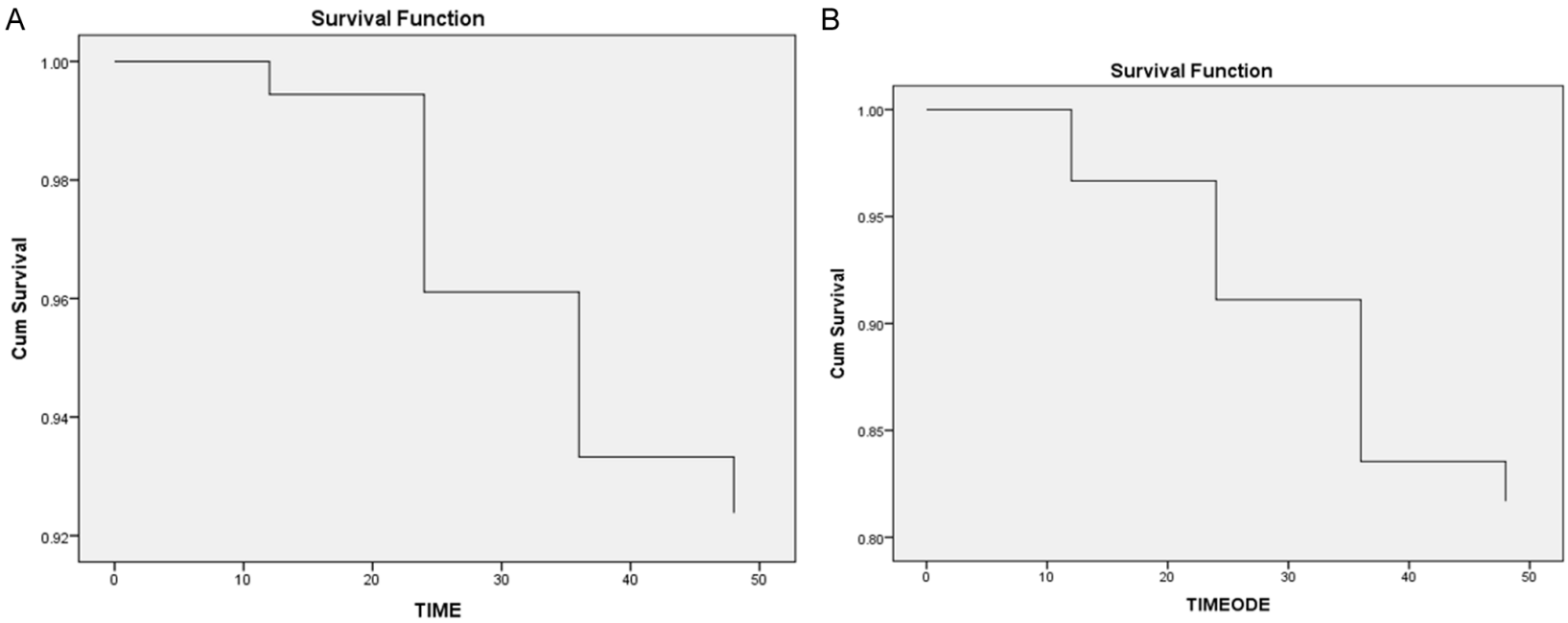

Figure 1. Life table of all and stage 1 endometrial cancer cases the table and schematic illustration of survival and recurrences prognosis after 4 years. (A) shows the survival rates based on mortality and (B) shows the survival rate based on recurrences.

recurrent endometrial cancer being a common factor among patients with mortality. This study also identified higher age and advanced stages as contributing factors [11]. Another report by Lortet-Tieulent and colleagues, examining endometrial cancer prevalence in the United States and Europe, discussed higher mortality rates among older patients and those with comorbidities such as diabetes and cardiac diseases [12]. Our study's results align with these reports, revealing a mortality rate of 8.9% and a higher risk of mortality in older patients, individuals with comorbidities, and those with advanced cancer stages.

Our present study also did not shed significant light on the importance of lymph node dissection in early-stage disease, as none of the cases in stage 1a exhibited positive lymph nodes. There were only three presumed-stage 1b cases with positive lymph node involvement, which led to upstaging of these patients and necessitated adjuvant treatments. Furthermore, we found that the number of dissected lymph nodes did not have a significant impact on patient prognosis. These findings align with the growing consensus on the need for sentinel lymph node mapping in presumed stage one endometrial cancer, particularly in stage 1b, to reduce surgical duration and minimize the adverse effects of complete lymph node dissection. While lymph node involvement has been shown to negatively impact survival rates in patients [13, 14], our data parallel the findings of Konno and colleagues in 2021. In Konno et al.'s study, lymphadenectomy was omitted for patients at low risk of lymph node invasion, and this approach had no adverse effect on survival [15].

Given that 176 cases (85.02%) in this study had pre-operative normal pap smears, the pap test appears to be an inadequate method for screening endometrial cancer or a reliable tool for anticipating cervical involvement in endometrial cancer cases. On the other hand, concerning the four positive pap-smear tests among our cases, we recommend evaluating the uterine cavity in cases with a suspicious history of abnormal uterine bleeding.

The noteworthy concurrence of micro-metastatic lymph node involvement in 10 out of 16 patients with positive lympho-vascular invasion (LVSI) could potentially serve as a valuable tool in deciding on adjuvant treatment, especially in cases where proper surgical staging, such as lymph node dissection, is not performed. However, it's important to note that further studies involving larger populations are recommended in this regard. In a 2021 study, Aslan and colleagues explained that there may be patients with occult lymph node metastases in the LVSI-positive group who were not evaluated for lymph node involvement. Therefore, the potential presence of occult lymph node metastasis represents a confounding factor when assessing the prognostic value of LVSI [16]. When assessing patients according to stage and histology criteria, we observed that LVSI had a negative impact on patient survival, which is contrary to the findings of a study by Dai et al. on 584 endometrial cancer cases in China. Dai and colleagues suggested that the influence of LVSI on survival may be dependent on other prognostic factors without independent predictive potential. They hypothesized that this difference could be attributed to regional factors or a lower threshold for adjuvant radiotherapy in China, which could obscure the negative prognostic value of LVSI [2, 17]. Given that risk stratification and treatment guidelines are primarily based on recommendations from Western-based studies, it underscores the need for well-designed prospective studies to develop a risk stratification system tailored to different populations.

The evaluation of various factors in this study revealed that a higher chance of survival could be expected in patients with younger age, lower tumor grade, less myometrial invasion, and histology of endometrioid carcinoma. While these findings are consistent with previous studies, there is ongoing debate regarding the prognostic value of factors such as lympho-vascular invasion (LVSI), lymph node dissection, cervical invasion, and adjuvant treatment [18]. Adjuvant radiotherapy is recommended for early-stage endometrioid carcinoma with high-risk or high-intermediate features [10].

Another noteworthy point is the presence of obesity as an important prognostic factor in most endometrial cancer cases, predisposing this population to higher mortality compared to the normal population, regardless of the underlying malignancy [10]. However, the present study did not align with this hypothesis. Although the highest mortality rate (62.6%)

occurred in cases with a BMI>30, and 41.7% of our cases had a BMI>30, we couldn't establish a significant correlation between BMI and mortality.

Furthermore, we observed higher mortality in cases with clear cell tumors and serous papillary histology, tumor size larger than 2 cm, and positive LVSI. In 2014, Vargas et al. reported that patients with myometrial invasion and higher stages (Stage 4) had higher mortality rates, and patients with larger tumor size had lower survival rates [19]. Another study by Lee and colleagues in 2012, based on 10 years of experience with 248 patients, showed that 5-year disease-specific survival for patients with stage I, II, III, and IV disease was 95.6%, 93.8%, 69.8%, and 50%, respectively. Age, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage, and histopathology were independent predictors of disease-specific survival [20]. The results of the present study are in line with previous reports, although this study is one of the limited surveys on patient mortality and associated factors in our region.

Our data indicate that regular follow-up using cervical pap-smear had no significant effect on detecting recurrent cases. Most recurrent malignancies were observed in the vaginal cuff and lungs and were diagnosed through speculum or bimanual examinations, abnormal bleeding, or pulmonary symptoms. These findings underscore the importance of conducting bimanual physical examinations and evaluating pulmonary signs and symptoms during surveillance. Therefore, recommending regular chest X-rays (CXRs) in surveillance is justifiable. However, determining the exact cost-effectiveness of this recommendation for early diagnosis of recurrent malignancies and its impact on patient survival rates requires further studies.

These data carry significant clinical relevance and are consistent with previous studies. While this study provides valuable insights into the outcomes of patients with various histological types and grades, it is important to acknowledge certain limitations. Firstly, the absence of grouping based on histological type and grade may limit the depth of our analysis and the ability to draw subtype-specific conclusions. Secondly, the cross-sectional design of the study restricts our ability to establish causal relationships between variables and outcomes. Additionally, the reliance on retrospective data may introduce biases and inaccuracies inherent to such data sources. Future studies incorporating prospective, longitudinal designs and stratified groupings based on histological characteristics could provide further clarity and depth to our understanding of the factors influencing patient outcomes in this context.

Conclusion

Based on our research, the mortality rate among patients was 8.9%, and we observed higher mortality rates among older patients, those with clear cell tumors and serous papillary histology, and those in higher cancer stages. Additionally, patients with comorbidities like diabetes and cardiac diseases, tumor size larger than 2 cm, and lymphovascular space invasion (LVSI) were also associated with higher mortality rates. Given these findings, it is increasingly important to consider individualized management strategies based on established prognostic factors, baseline genetic predisposition, or predictive biomarkers for endometrial cancer patients.

Disclosure of conflict of interest

None.

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