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ORIGINAL PAPER/GYNECOLOGY

Endometrial carcinoma in patients under 40 years of age: insights from the bulgarian cancer registry

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ABSTRACT

Objectives: We aimed to investigate the overall survival (OS) of young women with endometrial cancer (EC) in Bulgaria and the impact of histological type on survival.
Material and methods: This is a population-wide retrospective study of patients with EC (≤ 40 years at diagnosis) registered at Bulgarian National Cancer Registry (BNCR) between

1993 and 2020. Patients were re-classified according to the 8th edition of the TNM classification.

Results: In total, 30 597 patients were registered and histologically confirmed with malignant tumors of the uterine body. From that, 29 065 of them (95%) had ECs, and the rest had sarcomas. Around 1.64% of all malignant tumors of the uterine body are diagnosed in women under the age of 40. Most of them are diagnosed in the early stage. There was no significant difference in median OS for patients diagnosed before or after 2003. In recent years there was a slight improvement in survival and patients from the last cohort of this study had a 5-year survival rate of 92.5%. Patients with favorable pathology (T1, G1/2) had no lymph node involvement at the time of diagnosis and their 10-year survival rate was 94%.

Conclusions: EC in young women is a rare disease. In most cases, patients are diagnosed in early stageT1, G1/2, N0 and their prognosis is excellent. However, the lack of improvement of OS of young patients with EC in the last three decades shows the need for treatment optimization.

Key words: endometrial cancer; young women; rare diagnosis; epidemiology; incidence rates; survival

INTRODUCTION

A total of 417 326 new cases of malignant disease of the uterine corpus were diagnosed in 2020 worldwide. The incidence rate is more than double in Central and Eastern Europe and North America compared to the other regions in Europe [1]. EC is the most commonly diagnosed gynecological tumor in the United States in women over 65 years of age [2]. Malignant neoplasms of the endometrium include EC and uterine sarcomas. Historically the incidence rate of sarcomas was estimated to be between three and seven percent of all endometrial malignancies [3]. The natural history of the two malignancies and treatment approaches are very different [4], but due to the small rate of sarcomas in some epidemiological studies, they are often analyzed together.

EC has been further classified into two main clinicopathological and molecular types: Type I and Type II [5]. Type I is the endometrioid type [6]. The risk factors for its development are obesity, polycystic ovarian syndrome (PCOS), anovulatory cycles, irregular menstruation that causes hyperestrogenic state. This type of EC has a favorable outcome due to minimal invasion in the myometrium [7]. Type II EC is associated with higher patient age at presentation, high stage and grade, non-endometrioid histology, and poor prognosis [5]. It includes several subtypes such as serous, clear cell and undifferentiated carcinomas [8].

EC occurs mainly in menopausal women, and its incidence increases with age [9]. The average age of diagnosis is 65 years [2]In patients diagnosed under 40 years of age (≤ 40 years) EC is rare disease. According to various sources, between two percent and 14% of EC patients are young adults [4, 10–14]. There is a limited number of studies involving a small number of young women with EC [2]. These studies includes women up to 40 or 50 years of age at diagnosis [2]. EC patients tend to have a higher incidence of obesity (52–58%), nulliparity, infertility, irregular menstruation, and diabetes [10–12, 15]. In some regions an increase in the incidence of EC in young patients has been observed [16]. In most cases, EC is associated with the high levels of estrogen, while in a smaller proportion pathogenesis is associated with mismatch repair abnormality or Lynch syndrome [9].

Patients diagnosed with EC at a younger age have lower risk of recurrence [17]. Good treatment results in young patients are typical for the disease and usually due to its favorable histological characteristics. However, this group also includes patients with an aggressive phenotype, and heterogeneous treatment [18–20]. A better understanding of the clinical and morphological characteristics of this disease would lead to improvement of treatment. Bulgaria is one of the very few countries in Eastern Europe and the only country at the Balkans that has a national cancer registry. It was established in 1952. The electronic records database of the registry was created in 1993. From 2011 Bulgarian National Cancer Registry (BNCR) is collecting information regarding the applied treatments and data on disease progression [21].

Objectives

We aimed to investigate the demographic characteristics and overall survival (OS) trends in young patients (≤ 40 years) withEC registered in BNCR for the last three decades (from 1993 to 2020); the 5 and 10-year survival rate and the impact of histological types on survival.

MATERIAL AND METHODS

Study population

This is a population-wide retrospective study of patients with endometrial malignancies diagnosed up to and including the age of 40 and registered at the BNCR. For the study period a total of 31 546 women had been registered. Of these, 623 were under the age of 40. In 106 (17%) of them the pathological report showed sarcoma of the uterus and in 517 (83%) patients EC. All patients were re-classified according to the 8th edition of the TNM classification. The patients' flowchart is presented in Figure 1.

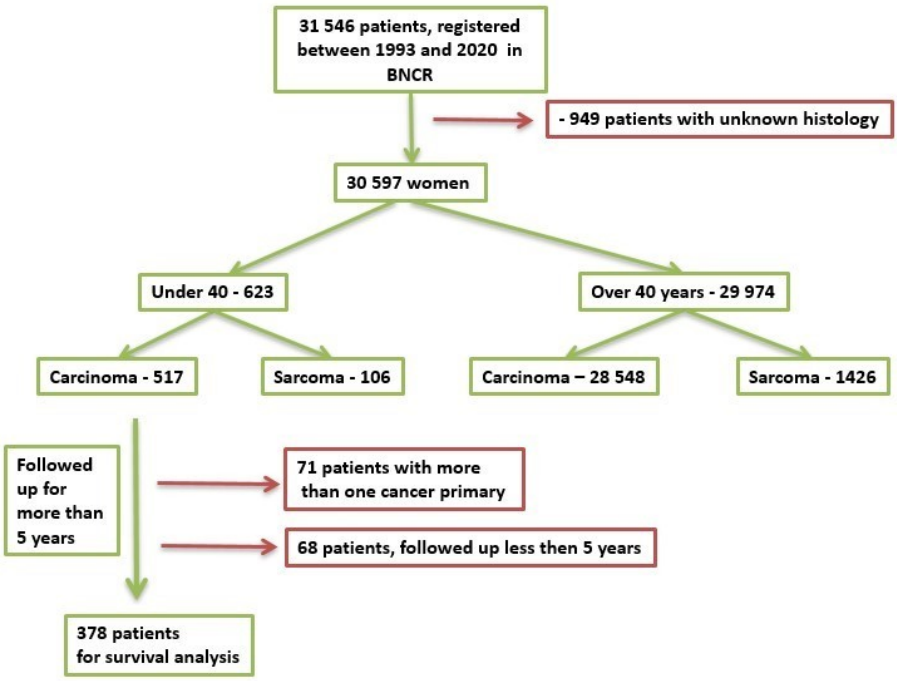

Figure 1. A flow chart of patients included in the study; BNCR — Bulgarian National Cancer Registry

Excluding criteria for survival analysis

From all 517 patients diagnosed under the age of 40 139 were excluded from the survival analysis: 71 patients diagnosed with more than one primary tumor; 68 patients who were followed up for less than five years. In the final survival analysis were included 378 patients. All patients were followed up until 1st January 2021.

Pathological characteristics

All patients were re-staged according to the 8th edition of the TNM classification. The impact of clinical and morphological parameters such as age, histological type, stage, grade, and lymph node on survival was investigated.

Data analysis

Statistical analysis was performed using SPSS for Windows v.22.0 (SPSS, Inc., Chicago, Illinois, USA). Continuous variables were described by mean and standard deviation (X ±

SD) in normal distributions or median and range (Me, Min ÷ Max) in asymmetric distribution. Categorical variables were measured on the nominal and ordinal scales and displayed as numbers and percentages. Median overall survival was computed using the Kaplan-Meier (log-rank test) method. The overall and 5-year survival rates in these patients were investigated, together with the relationship between survival and the listed clinical and morphological parameters. In reporting the results of this observational study, the STROBE guidelines for observational studies in epidemiology were followed.

Ethical approval

We received anonymous non-identifiable aggregate data collected from published registers and therefore an ethical committee approval to conduct the study is not required.

RESULTS

General data on endometrial malignancies

The incidence rate of EC in Central and Eastern Europe is traditionally the highest in Europe. According to the Global Cancer Observatory the age standardized incidence rate per 100 000 of EC in Bulgaria is slightly and constantly increasing since 1993 (Fig. 2). It was 14 per 100 000 in 1993 and 16.8 per 100 000 in 2013 [22].

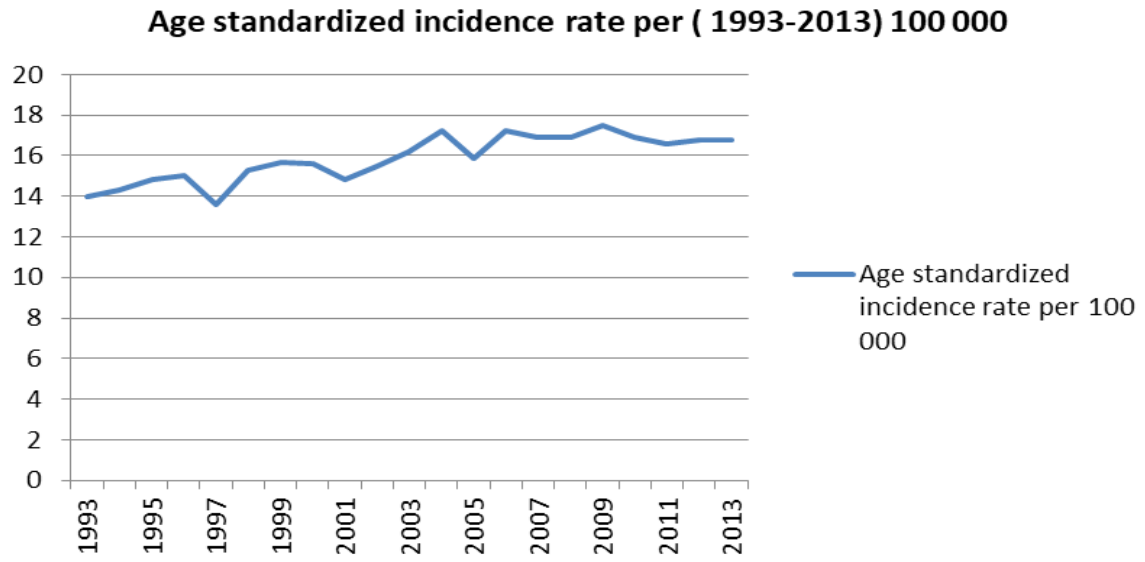

Figure 2. Age standardized incidence rate of endometrial cancer in Bulgaria 1993–2013

According to BNCR 30 597 patients with known histology were diagnosed with malignant tumors of the endometrium for the study period in Bulgaria (Fig. 1). Of these, 29 065 (95%) had EC, and the rest were sarcomas. Annually, an average of 1053 patients were

diagnosed with EC and 56 with sarcoma (Fig. 3). Even though the part of sarcomas of all malignant tumors of the endometrium was constant, there was a variation in the new incidence rate of sarcomas according to age group. In patients less than 40 years of age, sarcomas were diagnosed significantly more frequent and represented 16.6% of all newly diagnosed cases, compared to patients diagnosed after 40 years of age, where sarcomas represented only 4.5% of the total ($p < 0.0001$,Chi-Square test).

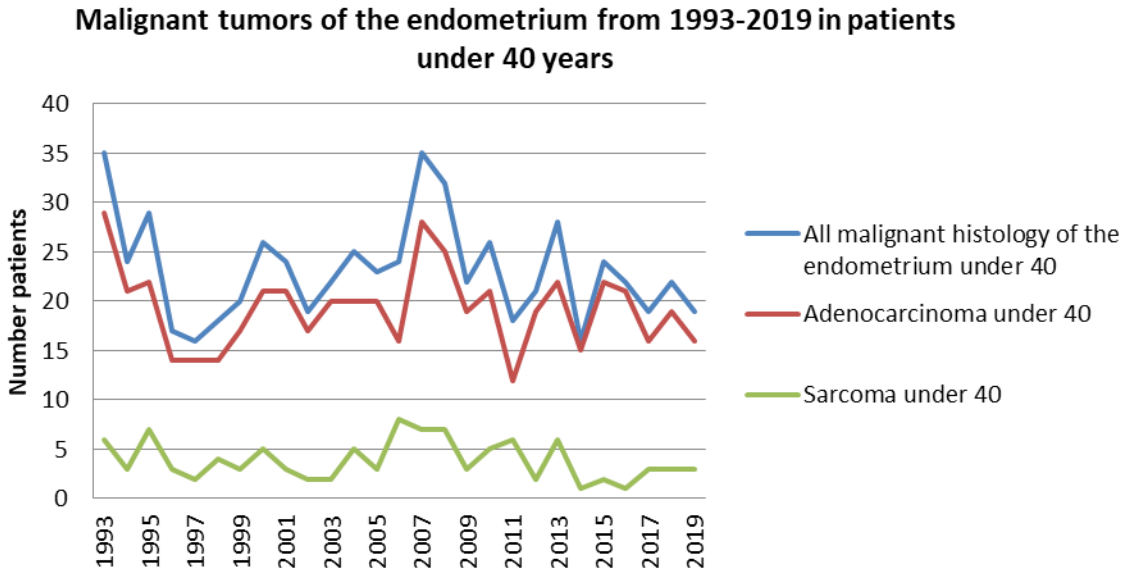

Figure 3. Annual incidence (absolute numbers) of newly diagnosed malignancies of the uterine body in women under 40 in Bulgaria between 1993 and 2019

Characteristics of patients under 40 years with endometrial cancer

Patients, diagnosed under the age of 40 years represented 1.64% of all malignant tumors of the uterine body. The mean age at diagnosis of EC among the patients in this group was 36.4 years, with the youngest patients diagnosed at the age of 20. The clinical and pathological characteristics of the young patients with EC are shown in Table 1. A total of 64.8% of the patients were without metastases in the lymph nodes. This was proved either by surgery or with imaging tests. Clinical staging was used in cases where only radiological staging by computed tomography was available. Also, 65.2% of patients were diagnosed in Stage I. Distant metastases at the time of diagnosis were found in only 0.8% (n = 4) of cases. 21 patients (4.06%) had synchronous endometrial and ovarian carcinomas.

Table 1. The characteristics of patients with endometrial cancer

Table 1. The characteristics of patients with CE.

Patients' characteristics	n	%
Total	517	100.0
Age groups		
16-20	1	0.2
21-25	7	1.3
26-30	36	7.0
31-35	111	21.5
36-40	362	70.0
Histological type		
Endometrioid tumor	420	81.2
Non-endometrioid	42	8.2
Unknown	55	10.6
Tumor Grade		
G1	162	31.4
G2	160	30.9
G3	20	3.9
Unknown	175	33.8
T stage		
T1	338	65.4
T2	116	22.4
T3	32	6.2
T4	4	0.8
Unknown	27	5.2
N status		
N0	335	64.8
N1	21	4.1
Unknown	161	31.1
M1	4	0.8
Stage		
Stage I	337	65.2
Stage II	110	21.3
Stage III	41	7.9
Stage IV	6	1.2
Unknown	23	4.4

Survival analysis

Patients with more than one primary cancer and patients who lived less than one month after diagnosis were excluded from the survival analysis.

5-year survival rate

A 5-year survival rate of the 378 patients diagnosed before 2015 was calculated. It is shown on Table 2. The 5-year survival rate improved over the years of the study by 5.5%, but the improvement of median overall survival was not significant ($p = 0.812$, log rank)

Table 2. The 5-year survival rate

Time period	5-year survival rate %	patients
1993–1997	86.9	84
1998–2002	88.3	77
2003–2007	91.5	82
2008–2012	89.0	82
2013–2015	92.4	53
Total	89.4	378

10-year survival rate of patients diagnosed before and after 2003

The 10-year median survival was compared between patients diagnosed before 2003 (including 2003) and after 2003. . The year 2003 was chosen as it was the tenth year since the set up of the BNCR, and therefore the 10-year survival could be calculated. There was a non-significant trend for better survival for the more recently diagnosed patients. Additionally, patients with favorable pathology (T1, G1/2) had no lymph node involvement at the time of diagnosis and 10-year survival rate of 94%.

Survival distribution according to stage

The analysis of 5-year survival included 378 patients, as 40 of them had died. The median survival was not reached. Patient's characteristics and 5-year survival rate are presented on Table 3. The Kaplan Meier curve on survival by stage is shown on Figure 3. The median overall survival in patients with endometroid cancer was significantly higher than in patients with non-endometroid (log rank, $p < 0.001$). The results are shown on Figure 4.

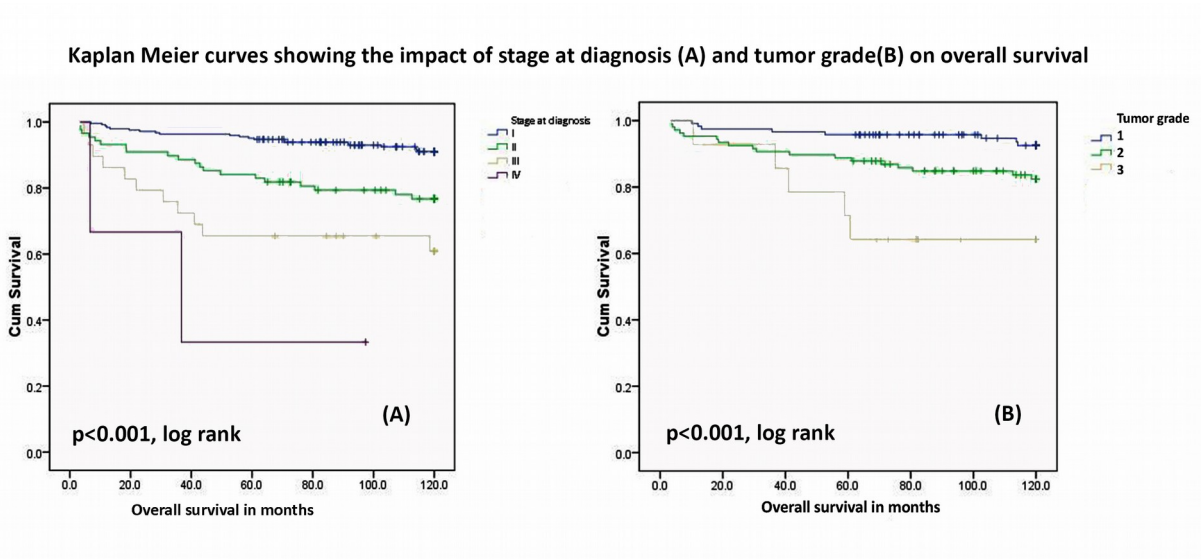

Figure 4. Kaplan Meier curve of overall survival according to stage at diagnosis and tumor grade

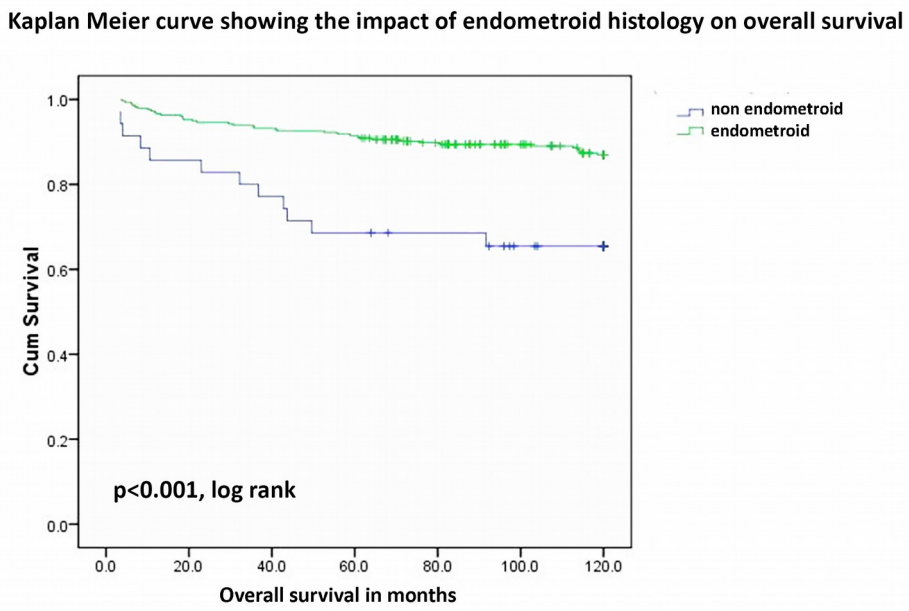

Figure 5. Kaplan Meier curve of overall survival of patients with endometroid vs non endometroid carcinoma

Table 3. Patients' characteristics and survival

Patient's characteristic	number patients	%	5-year survival rate %
Total	367	100.00	
Stage I	247	67.30	95.1

Stage II	88	23.98	84.3
Stage III	29	7.90	65.5
Stage IV	3	0.82	33.3
Grade	239	100.00	
G1	118	49.37	95.8
G2	107	44.77	88.8
G3	14	5.86	71.4
histology	331	100.00	
endometroid	296	89.43	91.6
non-endometroid	35	10.57	68.8

DISCUSSION

EC rarely occurs at an earlier age, making its correct diagnosis, treatment and follow-up, a clinical challenge. Nearly 15% of patients with EC are diagnosed under 50 years of age, and only 5% under 40 years [22]. One in five cases of EC under the age of 60 is diagnosed in women under the age of 40 [2]. Patients aged ≤ 40 years are considered to have more favorable clinical outcome, with a high survival rate of 96% and a chance of being referred for adjuvant therapy [2]. Lee et al. 2007 [23] showed that EC in women under 40 years is mainly endometrioid adenocarcinoma, which is also seen in our patients, while papillary serous carcinoma is significantly less common than in adult patients. However, this pattern is not consistent across the scientific literature [24]. Data on the stage of disease at diagnosis and the lymph node status are also contradictory [12, 19]. One of the most extensive studies on the subject founds that 79% of women under 40 are diagnosed in Stage I.

The primary method of EC treatment, regardless of age, is surgical and includes hysterectomy with bilateral adnexectomy and assessment of pelvic and paraaortic lymph node dissection. Frequently, patients with endometrial cancer under 40 years of age have not fulfilled their reproductive plan, thus requiring conservative treatment. Patients suitable for conservative treatment should: have a strong desire to preserve fertility potential; be at an age younger than 40 years at diagnosis; nulliparous; [1]; with Grade 1 tumors (but some series allowed Grade 2 [25]); have pre-expressed progesterone receptor (PgR) (even that some institutions do not perform PgR or estrogen receptor (ER) analysis [25–27]); normal serum levels of CA125 (< 35 U/mL); be at clinical stage IA [28] with the absence of myometrial,

cervical invasion, or extrauterine spread by some imaging cri-teria [vaginal ultrasound or computed tomography/magnetic resonance imaging (MRI)] and are reliable for follow-up. More recurrences and shorter progression-free survival are observed in patients receiving fertility-sparing treatment [3], without affecting the OS [2]. During the time of this study fertility-sparing surgeries were not performed in Bulgaria.

However, conservative treatment is often unsuccessful, and a small number of patients become pregnant. Different authors present inconsistent recurrence rates after such treatment: Ramirez et al. 2004 [29] report 19% recurrence rate after a complete therapeutic response and 23% in the group with no therapeutic response; while Ushijima et al. 2007 [30] report 47% recurrence rate after a complete therapeutic response. Therefore, conservative treatment must be considered very carefully in a multidisciplinary approach [31].

An additional feature of EC in young patients is the high frequency of synchronous endometrial and ovarian carcinoma. This frequency varies between 10–29% [12, 18, 32]. In these cases, EC is usually diagnosed at an earlier stage, with better differentiation, smaller tumor size, smaller myometrial invasion, and negative lymphovascular invasion, and even ovariancarcinoma also has a better prognosis [33–36]. In our study, 21 patients (4.06%) with synchronous endometrial and ovarian carcinomas were identified, which is a much lower incidence than reported in the literature. This could be due to the fact that these studies included on older patients — up to 45 or even 50 years of age. The presents of synchronous ovarian carcinoma in young patients with EC does not affect the OS. However, ovarian preservation may be considered in young patients for its benefits. [37, 38].

In the present study, EC is most common in the age group of 36–40 years, followed by the group of patients between 31 and 35 years. Over 90% of the cases are in patients over 30 years of age. EC in women under the age of 40 represented 1.78% of all EC, which is significantly lower than reported in the literature and constant over time. This is most likely due to the fact that in the years of the study, obesity in Bulgaria was still not as common as in developed countries [39] and this is considered one of the most significant risk factors for the development of EC [24].

The histological distribution among patients was comparable with other reports as over 80% of patients have endometrioid endometrial adenocarcinoma. However, the rate of patients diagnosed in Stage T1 — 65.4% is comparatively lower in our study. Nonetheless, a significant number of patients were diagnosed in the second stage (21.3%). This could be explained by delay in seeking medical help.

Over 60% of patients were G1 and G2. Lymphatic metastases were found in only 4.1% of cases and most of the patients were diagnosed in stage I, which are all factors associated with favourable prognosis. This is also confirmed by the overall 5-year survival rate of 89.4% for the patients in our study. Survival depends mostly on stage, grade, histology, and lymph node status and decreased significantly with the deterioration of histological parameters. Because of the low rate of lymph node metastasis (4.1%) and high rate of favourable prognostic factors in these patients, the sentinel lymph node dissection is a very reasonable approach. Thus, the patients can be staged accurately, avoiding the risk of complications of total lymph node dissection [40].

As a rare disease, the management of EC under the age of 40 is inconsistent and centre specific. Over the years, there has been no significant improvement in survival of patients with EC. Nevertheless, it remains relatively high. We believe that this is due to the more radical surgical treatment in almost all patients (without fertility-preserving surgery). Additionally, most patients underwent postoperative radiotherapy, as this was the standard treatment protocol in Bulgaria for this period. The excellent prognosis of these patients raises the question of treatment de-escalation through preservation of the ovaries and the sentinel lymph node biopsy.

Study limitations

Data from the BNCR are quite inconsistent with many missing variables. We could not identify the number of cases with negative lymph-node involvement where a lymph node dissection has been performed and in how many cases the lymph node status was determined clinically or by diagnostic imaging methods. We also lack information regarding the BMI, the clinical symptoms leading to diagnosis, reference to family history and how many cases were associated with hereditary syndromes. This study highlights the need to start including such data in the future.

CONCLUSIONS

EC under 40 years of age is a rare disease. In most of the cases patients are diagnosed in early stage — T1, G1/2, N0. In these patients the prognosis is excellent. However, the lack of improvement of the overall survival of young patients with EC in the last three decades shows the need for optimization and the good survival rate – room for de-escalation of treatment

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare no competing interests.

Data availability statement

Authors declare that all related data are available concerning researchers by the corresponding author's email.

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