RISK FACTORS AND CLINICAL SPECTRUM OF ENDOMETRIAL CANCER

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ABSTRACT

Background: Endometrial carcinoma (EC) is the second most common gynecologic cancer worldwide and most cases (75%) are diagnosed. Aim of study: Identifying the epidemiology and the risk factors of the disease based on the clinical manifestations, staging, and therapeutically approaches to endometrial cancer. Materials and Methods: A retrospective cross-sectional study conducted in National Cancer Institute, Misurata, Libya where 61 women were diagnosed with endometrial cancer between 2015-2017.The data of the patients were obtained including: age, symptoms, parity, abortion, past medical history, passive smoking, weight, staging, and treatment procedures. The mean age of the studied patients with endometrial cancer was 61.9 ± 11.4 years. The maximum age of the patients was 78 years and the minimum age was 35 years. The most common age group of patients was 56-65 years. The most common symptom was vaginal bleeding (83.6%), while weight loss (8.2%) and pelvic pain with constipation accounted for (5%). Most of the cases were grand parity 70%, and nearly 40% of women have shown history of abortion. Additionally, 13% of patients had an experience with passive smoking, 64% had diabetes and hypertension, and 73.7% of cases were obese. All of the cases were at stage II or more advanced during diagnosis, and about 40% of cases underwent surgery as a first-choice treatment. We have observed the association of abnormal vaginal bleeding and abnormal vaginal discharge with endometrial cancer. The study revealed many risk factors of the disease such as obesity, diabetes mellitus and hypertension. Understanding the epidemiology of the disease may assist with the treatment and the prevention strategies as well.

KEY WORDS: Endometrial cancer, Risk factors, Epidemiology, Staging.
ABBREVIATIONS: EC: Endometrial Cancer, UTI: Urinary Tract Infection, B.S.O: Bilateral Salpingo Ooophorectomy.

INTRODUCTION

Endometrial cancer defined as any invasive neoplasm of the uterine corpus. Invasive neoplasms of the female pelvic organs account for almost 15% of all cancers in women.(1) The most common of these malignancies is endometrial cancer. An estimated 54,870 cases are diagnosed annually, leading to 10,170 deaths. It is the fourth most common cancer, accounting for 7% of female cancers. Endometrial adenocarcinoma is the most common gynecologic malignancy in the United States. Fortunately, the majority of patients present at an early stage, resulting in only 4% of cancer deaths in women.(2) Uterine sarcomas comprise <9% of cancers of uterine corpus, however it is associated with more aggressive behavior and a poorer prognosis.(3)

The median age of occurrence is 63 years, while >90% of women are older than 50(3). Roughly, 75% of women survive for 5 years as most women are being diagnosed at an early stage because of irregular vaginal bleeding. At diagnosis, 75% of women have disease confined to the uterus (stage I). Five-year survival for stage I patients is 90%. In some cases, a history of complex hyperplasia/atypia can be demonstrated. The majority of endometrial cancers occur after menopause, but up to 25% of cases may be premenopausal.(4)

Endometrial cancer is commonly grouped into 2 different profiles with distinct risk factors.(5,6) Type I (80% of all cases) is believed to be hormone-related and to be significantly associated with both unopposed estrogen therapy and obesity. Type 2 endometrial cancer, which is less common (20% of all cases), consists of less common histological subtypes such as papillary serous, clear cell, mucinous, and carcinosarcoma. This second group is usually not associated with excess estrogen exposure. (7)

Most endometrial cancers still appear to be sporadic, except for about 10% that are hereditary.(8) Among genetically predisposed women, HNPCC syndrome is the most frequently encountered syndrome. Their risk of developing cancer is about 10 times higher than the baseline rate in the general population. (9) Patients with a personal history of breast, ovarian, or colon cancer also have an increased risk of developing a subsequent endometrial cancer.(10) Obesity and physical inactivity are also very important risk factors in the development of endometrial carcinoma.(11) Diabetes is also a risk factor, because hyperadrenocorticism is increased by hyperinsulinemia, which disturbs estrogen metabolism.(12) Tamoxifen is also a causal factor in the pathogenesis of endometrial cancer and can increase the risk as much as 6- to 8-fold. (13)

The surgical approach for the treatment of endometrial cancer has traditionally been laparotomy. Nevertheless, in the last 15 years, the use of minimally invasive techniques has been widely accepted by many authors. A recent publication of the Gynecologic Oncology Group (GOG) LAP2 study has shown similar operative outcomes in the minimally invasive surgery and in the laparotomy group. Laparoscopy seems to provide equivalent results in terms of disease-free survival and overall survival compared with laparotomy,

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with further benefit: shorter hospital stay, less use of painkillers, lower rate of complications and improved quality of life. A potential enhancement to laparoscopy has been provided by the robotic approach with a high 'benefit' in obese women. Since 2002, the use of robotic assisted laparoscopy has advanced rapidly, particularly in the United States. The largest published series of robotic surgery was reported in 2011 by Paley et al.[14] The major complication rate was significantly less with robotic surgery (20% versus 6.4%) compared with laparotomy, particularly related to wound complications and infections.

Due to the short data on endometrial cancer in Libya, we have investigated the epidemiology of the disease including the risk factors, the clinical manifestations, the histopathological staging, and the treatment.

Materials and Methods:

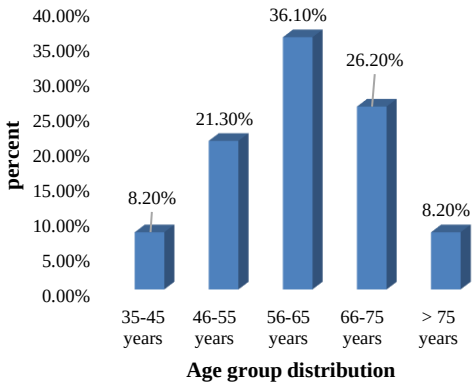
Methodology: A retrospective cross-sectional hospital record based study was conducted in the National Cancer Institute, Misurata, Libya from the period from 2015 to 2017. Sixty-one cases of women diagnosed with endometrial cancer were collected. The clinical data of the patients were reviewed from their records that included the age, sign and symptoms, parity, abortion, past medical history, smoking, weight, diagnostic methods, staging, and the treatment procedures. The ethical committee of NCI-Misurata approved the study, and the patients signed the consents.

Statistical analysis:

Statistical analysis was computerized using the Statistical Program for Social Sciences (SPSS version 22) that used for data entry and analysis. Descriptive statistics were used and all results are presented as frequencies, means ± standard deviation and percentages.

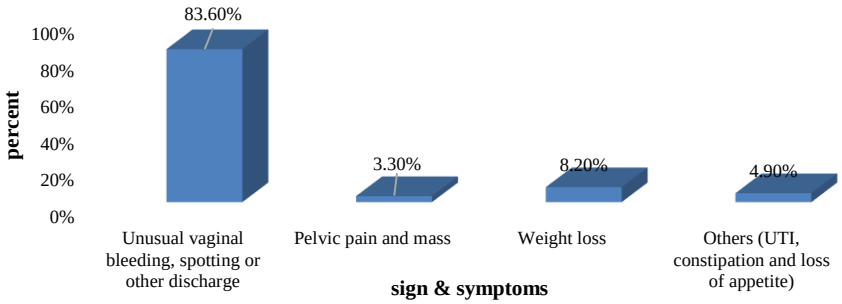
Results:

Age group distribution: The age distribution of the patients was illustrated in (figure 1). The age group of 56-65 years was the highest (36.1%), followed by the age group of 66-75years was (26.2%), with a mean age group of 61.92 ± 11.47(35-78) years.



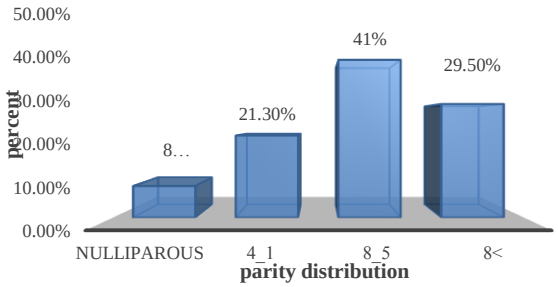
(Figure 1) Age group distribution of the studied endometrial cancer patients.

Symptoms of endometrial cancer: The most common symptoms of patients observed in this study were vaginal bleeding (83.6%), weight loss (8.2%), pelvic pain (3.3%), , and other symptoms (5%) (figure 2).



(Figure 2) The distribution of the symptoms of endometrial cancer patients.

Parity distribution: The mean parity of the patients in this study was 6.5 ± 3.6. Concerning the parity distribution, 41% of cases were from 5 to 8 parity, 29.5% were more than 8 parity, 21.3% were 1 to 4 parity, and 8.2% were nulliparous (figure 3).

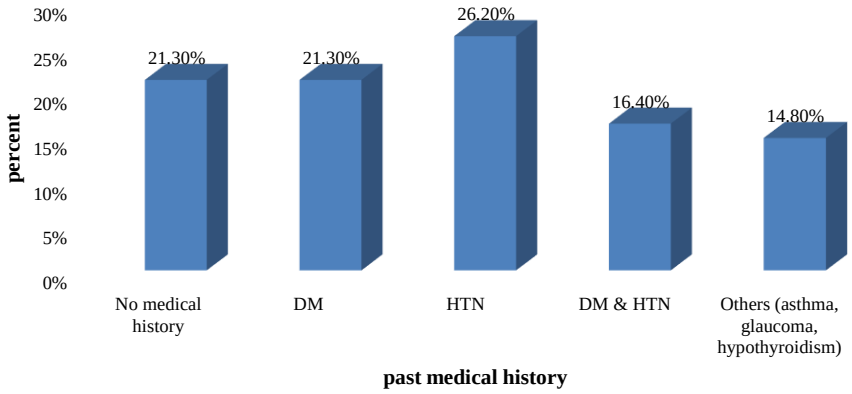


(Figure 3) Parity distribution of endometrial cancer cases.

Abortion history distribution: The abortion history among the studied cases was 39.3%, while 60.7% of patients had no history of abortion. The maximum times of abortion for a patient were 8 times.

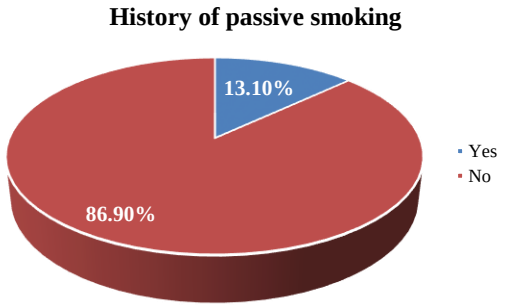
Past medical history of patients:

During the evaluation of the past medical history in the current study, nearly 64% of cases had hypertension (HTN) and diabetes mellitus (DM) 26.2%, and 21.3% respectively, while the women who had combined diabetes and hypertension were 16.4%. Other medical illnesses include asthma, glaucoma and hypothyroidism accounted for 15% of the cases. In contrary about 21.3% of the studied cases had no medical illnesses reported (figure 4).



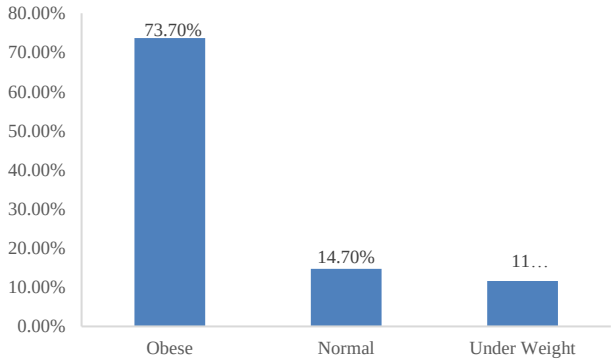
(Figure 4) The past medical history of endometrial cancer patients.

History of passive smoking: The passive smoking history among the studied cases was 13.1% (figure 5).



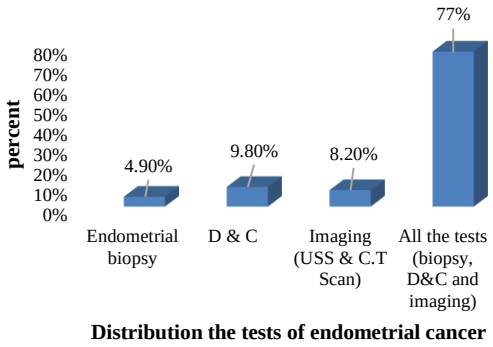
(Figure 5) History of passive smoking among the studied cases.

Weight of the patients' distribution: Most of the studied cases were obese 73.7%, while 14.7% had normal weight, and 11.7% had underweight (figure 6).



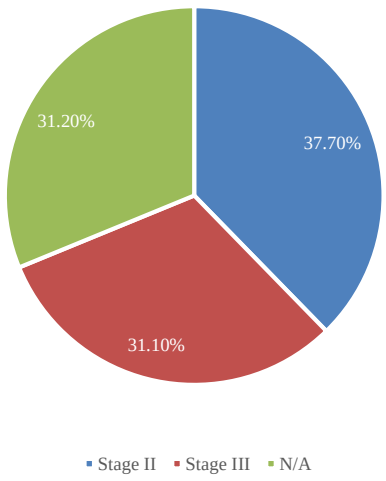
(Figure 6) Weight distribution of the patients.

The Diagnostic tests used for endometrial cancer cases: The studied cases of endometrial cancer were diagnosed by endometrial biopsies (4.9%), D&C (9.8%), and radiology imaging (8.2%). However, most of the cases (77%) were diagnosed by the three mentioned tests (figure 7).



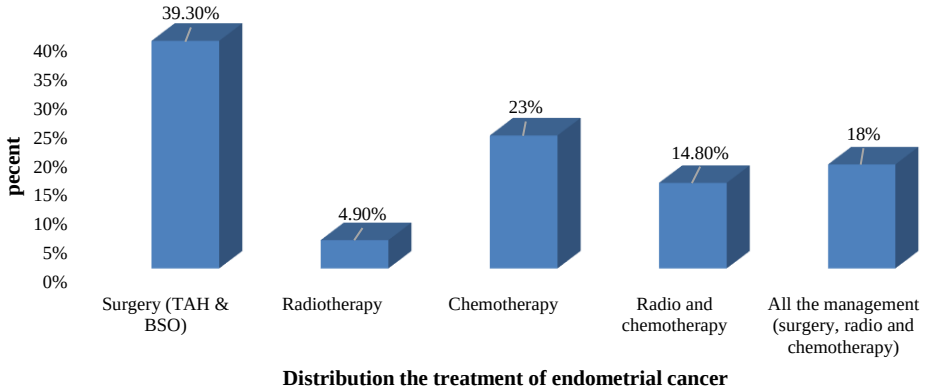
(Figure 7) Types of endometrial cancer tests.

Pathological staging of endometrial cancer: The studied endometrial tissues were subjected to staging of the tumors. The obtained results showed patients with stage II were 37.7%, and stage III were 31.1%. However, the staging of 19 cases was missing in their files. The staging was done according to FIGO (International Federation of Gynecology and Obstetrics) protocol (figure 8).



(Figure 8) Pathological staging of endometrial cancer cases.

The treatment management of endometrial cancer cases: This study showed that patients of endometrial cancer were treated by surgery (TAH +BSO) 39.3%, chemotherapy 23%, and by radiotherapy 4.9% of cases. The cases treated by both radio and chemotherapy were 14.8%, and the cases treated by the three mentioned therapies were 18% of cases (figure 9).



(Figure 9) The treatment managements of endometrial cancer cases.

DISCUSSION

Endometrial cancer (EC) is the most common gynecological malignancy estimated to affect over 54,000 new women in 2015. Despite the high incidence of EC, 70% of these malignancies are diagnosed at an early stage with localized disease confined to the uterus, and have a favorable 5-year overall survival approaching 95%. This early detection is often attributed b to the presence of disease-associated symptoms, such as abnormal uterine bleeding or vaginal discharge, which occur early in the disease process prompting evaluation. Although this observation is frequently referenced, there is little data in the literature documenting the prevalence of such symptoms in EC patients compared with the healthy population.[1]

The majority of women diagnosed with endometrial cancer are pre- peri- or postmenopausal between the ages of 35 and 78 years. The average age at diagnosis is 61.9 years. This finding was consistent with many other studies.[15,16] However, the risk of developing endometrial cancer increases with advancing age. For example, a woman under the age of 40 has a 1 in 1423 risk of developing the disease, but a woman older than 70 has a 1 in 81 risk [17]. In contrary the study of Andarieh M, and Delavar M (2016) showed less age group in their results, and the mean age was 52.9 years.[18]

Terry P and Vainio H (2002), revealed that endometrial carcinoma is relatively uncommon among women under 45 years old representing approximately 2–14% [19]. Our results were in agreement with this data, with a frequency of 8.2% from all cases below 45 years. According to the American Cancer Society, 95% of endometrial cancer affected women at age 45 years and older. The age of 60 years was the average age at diagnosis making the disease a significant threat to women's health in aging population. [20]

In regards to the symptoms at the presentation, the current study showed more than 80% of cases came with unusual vaginal bleeding. The second alarm symptom was weight loss with a frequency of 8.2%, followed by other symptoms such as constipation, UTI, and abdominal pain that existed in small frequencies of less than 5%. Those findings were inconsistent with the prior studies that have evaluated rates of general gynecological cancer alarm symptoms in large population-based studies. Low E et al.(2013) surveyed 911 women in the United Kingdom on the presence of gynecological cancer symptoms in the preceding 3 months, and found that 44% of respondents experienced at least one of the surveyed symptoms [21] .The most common symptoms reported were abdominal pain, back pain, or pelvic pain and increased abdominal size. About 21% of those surveyed reported three or more symptoms. With regard to potential endometrial cancer-related symptoms, 1% reported postmenopausal bleeding, and 5% reported abnormal vaginal discharge.[21] Another survey conducted in a healthy Danish population showed about 80% of respondents experienced at least one gynecological alarm symptom in the preceding 4 weeks along with nonspecific symptoms of tiredness, and abdominal bloating. Postmenopausal bleeding was reported in 2.3% of respondents, which was similar to the Low study. [22] These studies demonstrated that the prevalence of more specific gynecological alarm symptoms is relatively rare in the general population.

Various studies were in agreement with our findings, when patients specifically present with the gynecological warning symptoms of postmenopausal bleeding. Those studies have shown the risk of endometrial cancer to be 40 – 80%, and recurrent episodes of bleeding have been shown to be predictors of EC in addition to postmenopausal bleeding. [23,24] A study conducted by Balasubramaniam K et al.,(2014) found at age greater than 55, bleeding exceeded five pads per day, and recurrent episodes of bleeding significantly correlated with EC in postmenopausal women . Patients with EC were also found to have, on average, a longer duration of bleeding (63.3 vs. 9.0 days, $p < 0.01$). [22]

With respect to parity, many studies have shown that history of null gravidity was associated with elevated risk of endometrial cancer.[20,21,23] It is interesting that we found multiparous patients more when compared to nulliparous patients. The results of this study showed that there was a positive correlation between gravidity and endometrial cancer development. It was seen that majority of the cases reported here 70.5% were grand multiparous patients. The results observed in the study did not support the etiological hypothesis of hormonal mechanism of endometrial cancer.[24,25] Several studies have proved that women who experienced miscarriages and induce abortions have the half of risk of endometrial cancer as gravid women with no miscarriages and abortions. [17] The current study reported that almost 39.3% of women with endometrial cancer had experienced the abortion.

In addition, previous studies have suggested that women who smoke had lower risk of endometrial cancer than nonsmokers did. The greatest risk reduction was observed among heavy smoking women. [22] The present study showed that 13.1% of endometrial cancer cases had a history of passive smoking.

The current study reported that 73.7% were obese while about 64% of cases had either diabetes or hypertension or both. All of these findings were parallel with Burbos and Smith studies. [23,24]

The international guidelines and national protocols support a treatment approach of endometrial cancer consisting of surgery (i.e. surgical staging, total hysterectomy plus bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy, cytology, omenectomy, and maximal tumour debulking for the advanced carcinosarcomas), and adjuvant therapy.[19] Lymph node involvement will be found in 14-38% of carcinosarcoma patients undergoing lymphadenectomy and lymphadenectomy has been shown to provide significant survival benefit.[20] In the current study according to FIGO protocol most of the cases have diagnosed at the stage II or more of the disease. This may reflect the poor awareness among the patients. Many studies reported that early detection of endometrial cancer was due to screening and surveillance programs. [25]

In conclusion, the study showed the strong association of abnormal vaginal discharge and endometrial cancer. In addition, it found many risk factors associated with the disease including obesity, diabetes mellitus and hypertension. Understanding the epidemiology of this disease may aid with the treatment, and the development of prevention strategies in Libya.

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