Incidence of endometrial carcinoma diagnosed in the University Hospital of Split in regard to the COVID-19 pandemic

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INCIDENCE OF ENDOMETRIAL CARCINOMA DIAGNOSED IN THE UNIVERSITY HOSPITAL OF SPLIT IN REGARD TO THE COVID-19 PANDEMIC

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List of Abbreviations:

BRCA – breast cancer gene

CCC – clear cell carcinoma

CEA – carcinoembryonic antigen

COVID-19 – coronavirus disease 2019

CS – carcinosarcoma

EC – endometrial carcinoma

EEC – endometrioid carcinoma

FIGO – International Federation of Gynecology and Obstetrics

FSH – Follicle-stimulating hormone

LH – Luteinizing hormone

MC – mixed carcinoma

MMR – mismatch repair

Pap smear – Papanicolaou smear

PTEN – phosphatase and tensin homolog

pTNM – pathological Tumor, Nodes, and Metastases

RT-PCR – reverse transcription polymerase chain reaction

SC – serous carcinoma

UC – undifferentiated carcinoma

1. INTRODUCTION

1.1. THE UTERUS

1.1.1. Anatomy

The female reproductive system (Figure 1) is comprised of the ovaries, uterine tubes, uterus, and vagina and is in the lower abdomen between the rectum and urinary bladder (1). The ovaries are the female gonads, responsible for developing the oocytes and the production of reproductive hormones, which make them endocrine glands. Through the broad ligament, the ovaries are connected to the uterus. In differentiation to prepubertal females, in whom the ovaries are covered by a smooth layer of mesothelium, rendering them greyish and dull, the ovaries of females become progressively scarred after puberty and distorted due to repeating rupture of ovarian follicles. The uterine or fallopian tubes capture and escort the oocyte monthly and function as a connection between the peri-ovarian peritoneal cavity and the uterus. They are divided into four parts, beginning with the infundibulum, followed by the ampulla, the isthmus, and ending in the uterine part. Often, they are the site of fertilization (2). The uterus is a hollow organ with a thick wall composed of the endometrium, myometrium, and perimetrium (1). It is divided into the body and cervix, which are connected by the isthmus of the uterus. The myometrium, with its muscular properties, adapts to the growth of the fetus during pregnancy and works as a major muscle for the process of childbirth (2). Functionally, the endometrium undergoes various changes during the menstrual cycle, which are modulated by hormones, such as the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH) (1). When it comes to conception, the blastocyst implants in the endometrial layer, and if conception does not occur, the inner surface necrotizes during the menstrual phase (2).

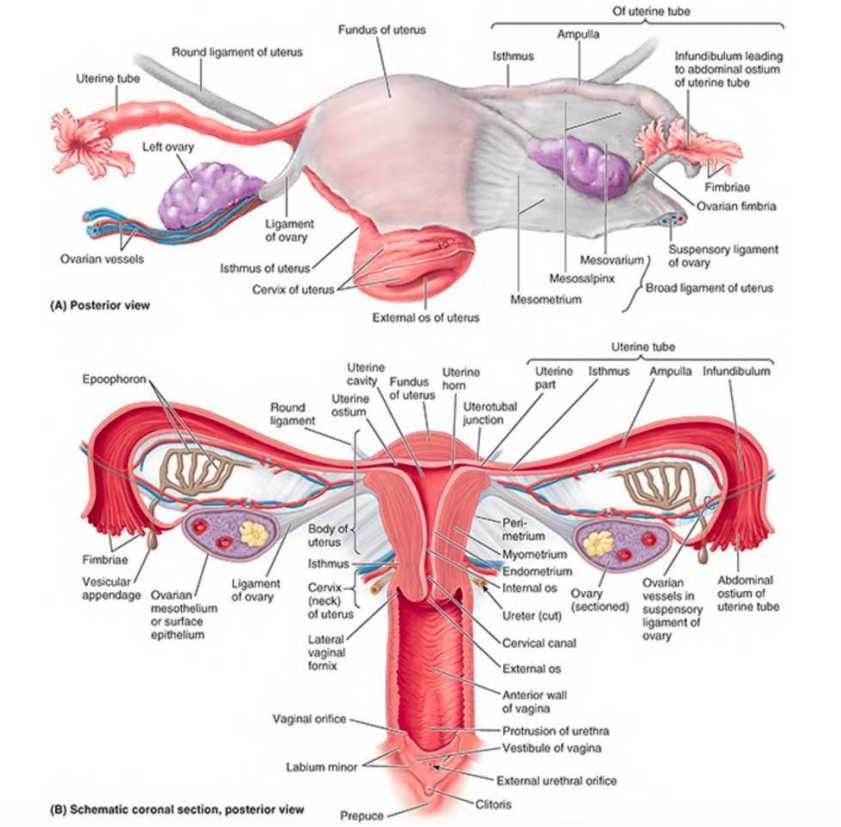

Figure 1. Internal female genital organs.

Source: Arthur F. Dalley, Anne M. R. Agur - Moore's Clinically Oriented Anatomy. Wolters Kluwer (2023) Date: 07.07.2024.

1.1.2. Embryology

The female reproductive system arises after the fifth and sixth week of fetal life from four different origins: the mesoderm, primordial germ cells, coelomic epithelium, and mesenchyme. Before this time, the genital system is indifferent to that of male fetuses. In the seventh gestational week, the paired paramesonephric ducts develop from focal invaginations of the coelomic epithelium, followed by the growth of the Mullerian ducts. From these paramesonephric ducts, the upper third of the vagina, the cervix, both fallopian tubes, and the uterus arise. During the eighth week, the paramesonephric ducts fuse vertically and eventually form the uterus with its endometrium and myometrium. The process of development of the uterus and other structures, derived from the Mullerian ducts, is completed by the end of the first trimester of pregnancy (3).

1.2. ENDOMETRIAL CARCINOMA

1.2.1. Epidemiology

Endometrial carcinoma (EC) is the most common gynecological cancer (5) and has its origin within the uterus' inner epithelial lining (6). Globally, 142.000 females develop endometrial cancer every year, and approximately 42.000 females die from this condition (7). Worldwide, disease-associated mortality and incidence are on the rise (6). Since 2020, in Europe, EC has been the fourth most common neoplasm in women (6), and its incidence peaks in the 6th and 7th decade of life (8). The majority, 75%, are diagnosed at an early stage and do not show signs of extra-uterine spread in preoperative scans (5). A percentage of 35 is diagnosed in an advanced stage and associated with a poor prognosis because of late occurring metrorrhagia (9). There is a significant difference in survival rates between women from various ethnic backgrounds. For white women, the 5-year survival rate reaches 84% at all stages, whereas for black women, it stands at 63% (10).

1.2.2. Etiology

Based on clinical, endocrine, and metabolic characteristics, the classification proposed by Bokhan's publication is used to differentiate two different types of EC. Type I tumors, caused by hyperestrogenism, are present in obese women and women suffering from diabetes or hyperlipidemia (11). Histologically, they are endometrial, with EEC being the most common form (12). In comparison, type II tumors are associated with non-obese women and are independent of endocrine or metabolic diseases. Due to their association with atrophic endometrium and their poor differentiation, type II tumors tend to be clinically aggressive, have a high tendency to metastasize, and are connected to an overall unfavorable prognosis (11).

Based on new molecular studies according to the Cancer Genome Atlas, there are four types of carcinomas based on their genomic characterization. The first group, leading to a good prognosis, includes polymerase epsilon (POLE) mutations. Group two has an intermediate prognosis and shows microsatellite instability. Associated with an intermediate prognosis as well is group three, displaying low-copy-number alterations. Lastly, group four includes TP53 mutations and high-copy-number alterations and leads to a poor prognosis. The classification of tumors has improved due to this genomic characterization and the identification of many gene fusions. Based on immunohistochemical and morphological features, it leads to less challenging diagnoses and better characterization (25).

1.2.3. Risk Factors

An increased risk of EC occurs with advancing age, higher BMI, endogenous and exogenous estrogen exposure, tamoxifen use, early menarche, late menopause, lower parity, metabolic syndrome, certain ethnic groups, as well as familial and genetic predisposition. In contrast, normal BMI, the use of oral contraceptives, and higher parity decrease the risk. Especially in developing countries, the growing prevalence of obesity is matched with that of EC. There is evidence that hyperglycemia and insulin resistance, associated with obesity and a high BMI, accelerate cell proliferation. An independent connection is made between EC and diseases such as diabetes mellitus and metabolic syndrome (6). The decreased incidence in parous women is explained by the hormonal changes during pregnancy. In that period, increased progesterone production, with its protective effect, positively influences the endometrium (13).

Another significant category encompasses genetic risk factors. The strongest correlation is with Lynch syndrome, characterized by a germline mutation in one of the mismatch repair (MMR) genes. Lynch syndrome is an autosomal dominant disorder caused by germline mutations in one of the MMR genes. Especially in premenopausal women, it plays a role in the association of EC (14). Additionally, mutations in the phosphatase and tensin homolog (PTEN) gene causing Cowden syndrome can increase the risk of developing EC. Cowden syndrome is additionally classified as an autosomal dominant disorder and causes not only EC but also thyroid cancer and breast cancer. In contrast, the findings in a study of women with endometrial cancer showed a low correlation to breast cancer gene (BRCA) mutations (6).

1.2.4. Histology

1.2.4.1. Endometrioid carcinoma

Endometrioid carcinoma (EEC), seen in Figure 2, usually presents with a glandular or villoglandular configuration lined with stratified columnar epithelium. Sharing a common apical border, the columnar lining cells build a glandular lumen. An eosinophilic and granular cytoplasm and a mild to moderate nuclear atypia are present with inconspicuous nucleoli, excluding poorly differentiated carcinomas. These poorly differentiated carcinomas show an altered endometrial stroma and a loss of intervening stroma (4).

The grading of EEC is mostly according to their configuration, from grade I to grade III: grade I with 5% or less of solid growth, grade II between 6 and 50%, and grade III with more than 50%. Between those three, grade I and grade II of EECs are considered low-grade,

while grade 3 is considered high-grade. Additionally, FIGO stage, histological grade, age, depth of myometrial invasion, and lymphovascular invasion are of crucial predictive value for the outcome. The depth of myometrial invasion is related to the risk of nodal spread and recurrence. In contrast, outer invasion is connected to decreased survival rates (4).

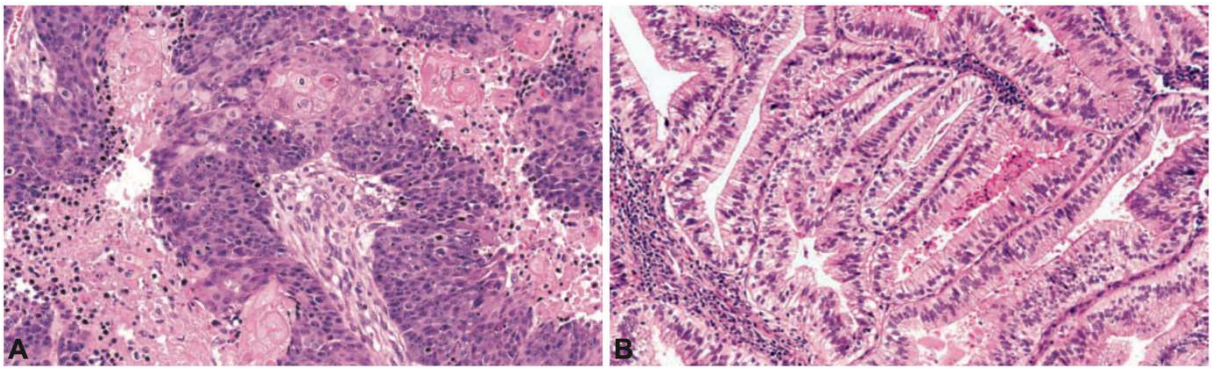

Figure 2. Endometrioid carcinoma. **A.** high-grade EC**. B.** EC with secretory differentiation.

Source: Kurman RJ, Caranglu ML, Herrington CS, Young RH. WHO Classification of Tumors of Female Reproductive Organs. 4th edition. Lyon International Agency for Research on Cancer (IARC) 2014 Date: 07.07.2024

1.2.4.2. Mucinous carcinoma

Mucinous carcinoma, shown in Figure 3, histologically presents with the same glandular or villoglandular architecture as EEC but exhibits a uniform, mucinous, columnar epithelium with minimal stratification. They often show squamous differentiation, low mitotic activity, and mild to moderate nuclear atypia. The mucin appears slightly pale or as basophilic globules with granular cytoplasm, which reacts positively to mucicarmine and carcinoembryonic antigen (CEA). Typically, myometrial invasion is confined to the inner half. The most significant distinction to EEC is the well-differentiated behavior and the relatively good prognosis of mucinous carcinoma (4).

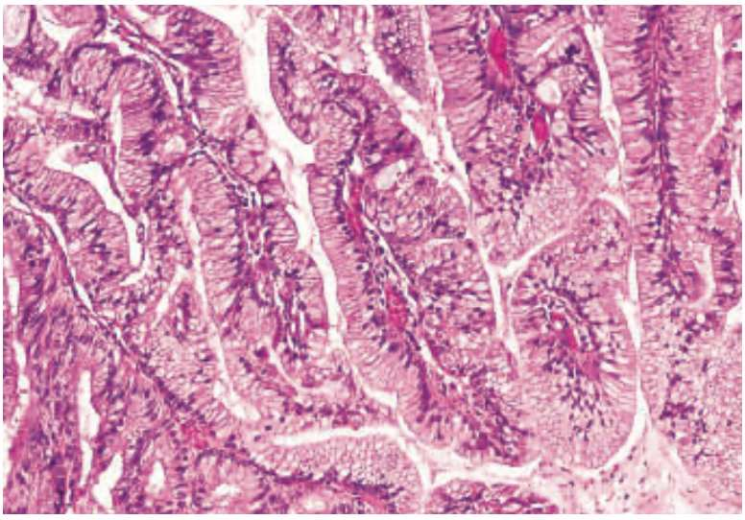

Figure 3. Mucinous carcinoma.

Source: Kurman RJ, Caranglu ML, Herrington CS, Young RH. WHO Classification of Tumors of Female Reproductive Organs. 4th edition. Lyon International Agency for Research on Cancer (IARC) 2014 Date: 07.07.2024

1.2.4.3. Serous carcinoma

Serous Carcinoma (SC), as seen in Figure 4, is the typical type II tumor. Histologically, it has a complex papillary configuration, with papillae varying from short, hyalinized, and branching to long, delicate, and thin, with marked nuclear pleomorphism. SC usually develops in atrophic endometrium or on a polyp, and even though it does not always present with invasion, it has the potential to metastasize extensively to extra-uterine sites. Due to these reasons, it is usually a high-grade EC and is connected to extra-uterine spread, which is almost always associated with recurrence and death (4).

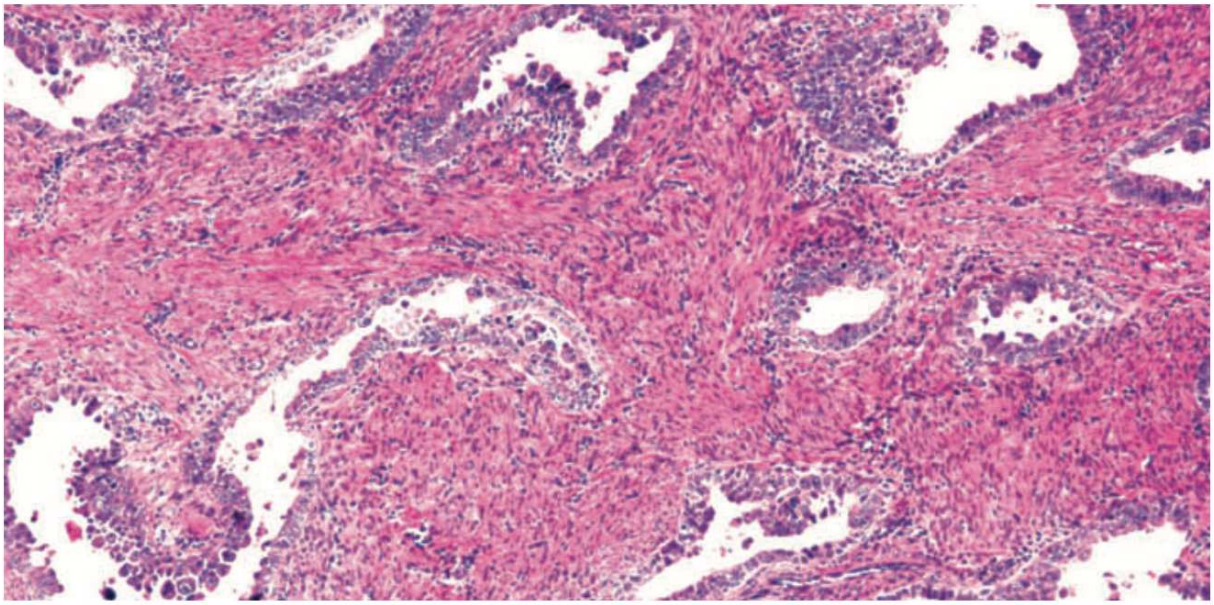

Figure 4. Serous carcinoma, gaping gland pattern.

Source: Kurman RJ, Caranglu ML, Herrington CS, Young RH. WHO Classification of Tumors of Female Reproductive Organs. 4th edition. Lyon International Agency for Research on Cancer (IARC) 2014 Date: 07.07.2024

1.2.4.4. Clear cell carcinoma

Clear cell carcinoma (CCC), shown in Figure 5, is composed of hobnail-shaped or polygonal cells with eosinophilic or clear cytoplasm exhibiting bulocystic, solid or papillary architecture. It is of high-grade nuclear atypia with numerous mitotic figures. As one of the type II tumors, their prognosis varies with survival rates from 21-75% and, regardless of stage, a 5-year survival rate of less than 50% (4).

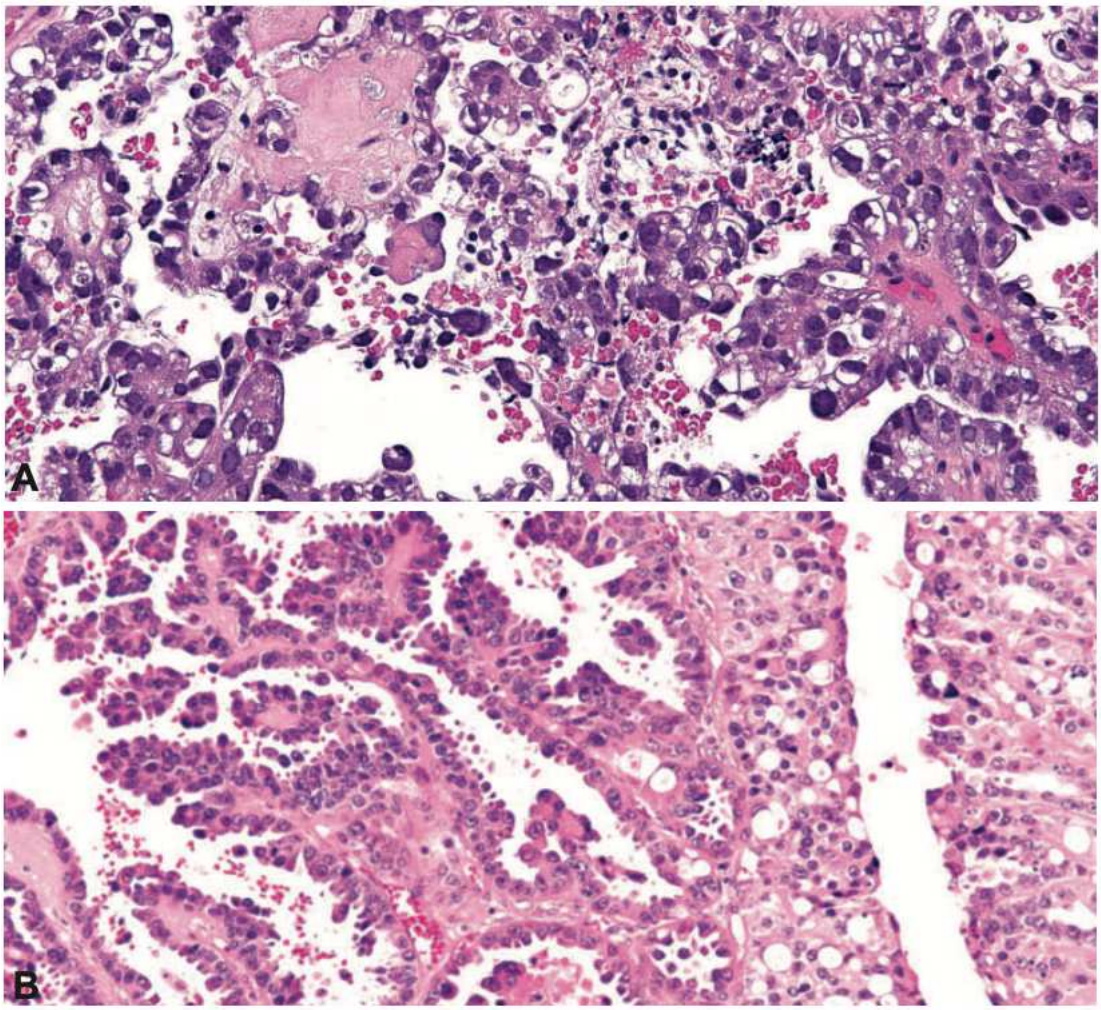

Figure 5. Clear cell carcinoma. **A.** Clear cytoplasm with hobnail cells. **B.** Papillary and solid patterns.

Source: Kurman RJ, Caranglu ML, Herrington CS, Young RH. WHO Classification of Tumors of Female Reproductive Organs. 4th edition. Lyon International Agency for Research on Cancer (IARC) 2014 Date: 07.07.2024

1.2.4.5. Mixed carcinoma

Mixed carcinoma (MC), seen in Figure 6, is histologically built from two or more different types of EC, of which one at least is of type II staging. Tumor markers such as PTEN, p16, and p53 help to distinguish between the two most frequent ones, endometrioid and serous carcinoma. PTEN expression is usually present in SC but lost in EEC, and while SC displays diffuse p16 staining and irregular p53 staining, EC only shows a patchy p16 distribution. These carcinomas are high-grade tumors, and according to their composition, their outcome varies (4).

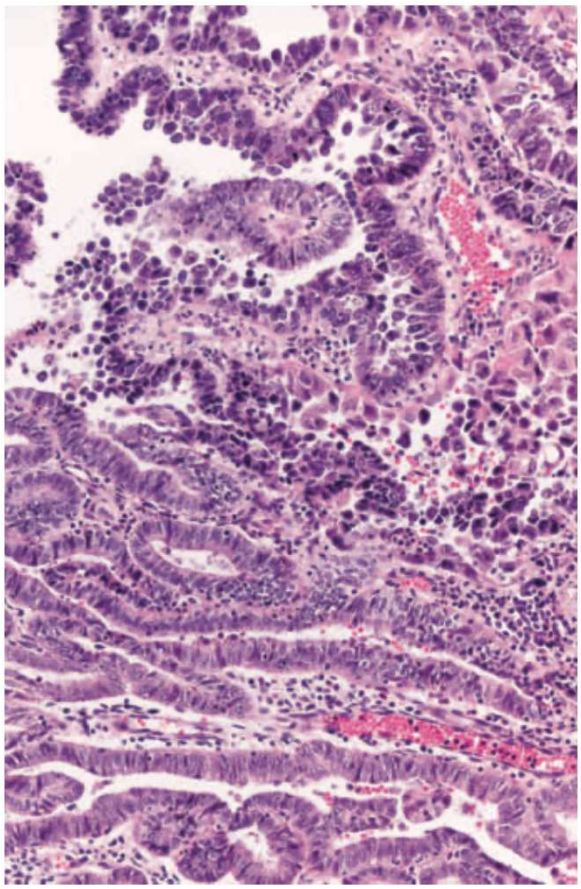

Figure 6. Mixed carcinoma.

Source: Kurman RJ, Caranglu ML, Herrington CS, Young RH. WHO Classification of Tumors of Female Reproductive Organs. 4th edition. Lyon International Agency for Research on Cancer (IARC) 2014 Date: 07.07.2024

1.2.4.6. Undifferentiated carcinoma

Undifferentiated carcinoma (UC) consists of dyshesive, small to intermediate-sized cells of uniform size, and it resembles lymphoma, small cell carcinoma, or plasmacytoma in their configuration. These tumors are considered highly aggressive due to their high number of mitotic figures and pleomorphic nuclei. In 55-95% of women, UC is associated with recurrence or death (4).

1.3. DIAGNOSIS OF ENDOMETRIAL CARCINOMA

In women with EC, there are only a few notable findings on physical examination. A gynecological examination of the vagina or cervix should be performed to evaluate the causes of abnormal bleeding, and the uterus and adnexa should be examined for unusual masses. No specific laboratory tests are available to aid in the diagnostic process of EC. They should still involve a pregnancy test for women of childbearing age and, if heavy bleeding is present, a complete blood count with prothrombin and partial thromboplastin time. Papanicolaou (Pap) smears are not part of a routine evaluation, but their result can indicate EC (15). For all postmenopausal women with benign endometrial cells present on the Pap smear, further testing is required, regardless of the symptoms present at the time (16).

To further evaluate the cause of abnormal bleeding, either endometrial biopsy or transvaginal ultrasonography is used (15). For detecting EC in an endometrial biopsy, the Pipelle device is a new sampling technique (17) with high accuracy (15). The sensitivity for post-menopausal women was calculated at 99%, and for premenopausal women, it was at 91% (17).

The advantages of either transabdominal or transvaginal ultrasonography are its noninvasiveness, safety (17), cost-effectiveness, and high sensitivity. For these reasons, they are usually the initial tests performed at suspicion (15), particularly to assess the need for further testing in postmenopausal women (16). It is used for the evaluation of the endometrial lining, especially its thickness. Endometrial thickness measuring less than 5 mm is rarely associated with a positive diagnosis (17).

As an additional diagnostic imaging tool, magnetic resonance imaging can provide information on structural abnormalities (15), and computed tomography can provide information about lymph node involvement (18).

1.4. STAGING OF ENDOMETRIAL CARCINOMA

Staging is the most important step in diagnosing EC to evaluate prognosis and treatment. It requires findings from a variety of medical fields, such as radiology, pathology, and surgery. The most common staging classification systems are the International Federation of

Gynecology and Obstetrics (FIGO) and the World Health Organization Pathological (pTNM) classifications (19).

FIGO separates EC into four stages according to histopathological findings (19).

Stage I ECs are limited to the ovary and uterine corpus. They are generally associated with a good prognosis, especially the Stage IA tumors, which are considered low-grade and non-aggressive forms. Stage IC is histologically more aggressive but still confined to the endometrium or a polyp (19).

Stage II ECs are divided according to invasion of the cervical stroma of histologically non-aggressive types as in stage IIA, substantial lymphovascular space involvement of histologically non-aggressive types as in stage IIB, and histologically aggressive types with any myometrial involvement (19).

Stage III is characterized by any local and/or regional spread, for example, to the uterine serosa, adnexa, fallopian tube, ovary, vagina, or pelvic peritoneum of any histological subtype. The presence of metastases of tumors in this stage makes them more aggressive and their prognosis worse (19).

Stage IV tumors are divided into stage IVA, with invasion of the bladder mucosa and/or the interstitial mucosa; stage IVB, with abdominal peritoneal metastasis beyond the pelvis; and IVC, with distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the lungs, liver, renal vessels, brain, or bone (19).

According to FIGO staging of EC, revised in 2023, low-grade EECs are considered non-aggressive histological types, while high-grade EECs, SCs, CCCs, UCs, MCs, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas (CS) are considered aggressive histological types (19).

The pTNM classification divides ECs into categories according to the extent of the tumor, the spread to regional lymph nodes, and metastases to distant sites. As shown in Table 1, it is closely associated with the FIGO classification (19).

Table 1. FIGO and pTNM classification of endometrial carcinoma

Definition	FIGO Stages	TNM Categories
Primary tumour cannot be assessed		TX
No evidence of primary tumour		T0
Tumour confined to the corpus uteri[a]	I[a]	T1
Tumour limited to endometrium or invading less than half of myometrium	IA[a]	T1a
Tumour invades one half or more of myometrium	IB	T1b
Tumour invades cervical stroma, but does not extend beyond the uterus	II	T2
Local and/regional spread as specified here:	III	T3
Tumour invades the serosa of the corpus uteri or adnexae (direct extension or metastasis)	IIIA	T3a
Vaginal or parametrial involvement (direct extension or metastasis)	IIIB	T3b
Metastasis to pelvic or para-aortic lymph nodes[b]	IIIC	N1,N2
Metastasis to pelvic lymph nodes	IIIC1	N1
Metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes	IIIC2	N2
Tumour invades bladder/bowel mucosa	IV	T4[c]

a Endocervical glandular involvement only should be considered as stage I.

b Positive cytology has to be reported separately without changing the stage.

c the presence of bullous oedema is not sufficient evidence to classify as T4.

1.5. TREATMENT OF ENDOMETRIAL CARCINOMA

1.5.1. Surgery

For EC, the most important therapy is surgery, which includes total hysterectomy, bilateral salpingo-oophorectomy, and possible omentectomy and lymph node dissection if the diagnosis suggests it. As an alternative to laparotomy, laparoscopy-assisted hysterectomy is preferred by experienced surgeons and applied in selected patients due to shorter hospital stays and decreased blood loss. Lymphadenectomy is considered beneficial if positive adnexal metastasis, serosal infiltration, or lymph nodes are present and in high-risk patients overall. Surgical cytoreduction and detailed lymphatic dissection are recommended for type II ECs due to their likelihood of extrauterine spread (18). Surgical re-staging can be considered in previously incompletely staged patients, and possible adjuvant therapy is discussed (20).

1.5.2. Radiotherapy

Radiotherapy for EC is used as adjuvant therapy. Radical radiotherapy is reserved for patients with inoperable tumors, but for them, it has the possibility to be curative. It can be either delivered externally, as vaginal brachytherapy, or as a combination targeting the abdominal region, the pelvis, or the paraaortic area (20).

Additionally, pelvic radiotherapy is used for local control if risk factors such as stage IC or age over 60 years are present and lymphadenectomy is not done during surgery. A combination of postoperative radiotherapy and surgery is associated with complications, which present in 1-10% of women depending on characteristics such as the general status of the patient or irradiation volume of the vagina, bladder, or bowel (20).

1.6. COVID-19

The coronavirus disease 2019 (COVID-19) was first detected in Wuhan, China, at the end of December 2019. Since then, it has spread worldwide, and on March 11th, 2020, the World Health Organization declared COVID-19 a global pandemic (21).

COVID-19 is a positive single-stranded RNA virus of the subfamily Coronavirinae. As a zoonosis, it is widespread among mammals and birds. The transmission from the animals to the human species happened through meat consumption at the Huanan wholesale seafood

market. Still, human-to-human transmission occurs through contact, airborne, or direct transmission (22).

Clinical signs differ between mild illness with non-specific symptoms, including fever, myalgia, and cough, to severe or fatal outcomes. The disease presentation showed a wide variety and different combinations of symptoms individually for each patient (22). First, shortness of breath and pneumonia were believed to be the primary causes of death among patients; nevertheless, evidence shows that thromboembolic events were the most severe manifestations at the time (23). Early disease detection is highly important and is done by reverse transcription polymerase chain reaction (RT-PCR) using swabs of the nasopharynx or oropharynx (22).

Initially, antibacterial therapy, antiviral therapy, and glucocorticoids were used as treatments for the primary infection, but immunocompromised patients and pregnant women required hospitalization. The turning point, however, was vaccine development (23). Vaccines are of high importance to prevent diseases and to establish herd immunity. Vaccine performance against COVID-19 is negatively affected by the constant viral mutations (24).

With epidemiological control came the reduction of hospitals' caseload. Only severely ill patients were treated further, and surgeries were held at a limit to reduce possible nosocomial outbreaks amongst hospitalized patients and healthcare workers (25).

2. OBJECTIVES

2.1. AIM OF STUDY

1. To determine the incidence of endometrial carcinomas operated and diagnosed in University Hospital of Split before, during, and after the COVID-19 pandemic.
2. To investigate gross and histological characteristics of endometrial carcinomas in three studied groups in regard to the time of the COVID-19 pandemic and to compare them.
3. To determine the stage of the disease at the time of diagnosis according to pathological pTNM stage by World Health Organization classification of female genital tumors, as well as FIGO classification, for each studied group and to compare them.

2.2. HYPOTHESIS

We propose the hypothesis that due to COVID-19, fewer surgeries were performed for patients with EC during the time of the pandemic. Consequently, we expect gross and histological findings to indicated larger tumors, more aggressive histological type of endometrial carcinomas, as well as more advance stage of the disease in the group after the end of COVID-19 restrictions.

3. PATIENTS AND METHODS

3.1. PATIENTS

This study included 218 patients diagnosed with endometrial carcinoma, who were operated at the Gynecological Department of the University Hospital of Split. Altogether, the data from 220 patients was investigated, but two patients were excluded due to their diagnosis of carcinosarcoma. The surgical material was evaluated and graded according to their histological appearance by the Pathology Department at the same hospital from January 2018 until March 2024. The participants were divided into three groups, according to the date of diagnosis. The first group before COVID-19 was from the 1st of January 2018 until the 31st of December 2019. The second group during COVID-19 was from the 1st of March 2020 until the 1st of March 2022. The third group after COVID-19 was from the 1st of March 2022 until the 1st of March 2024. Information about the location and size of the tumors, histological grade - and type, involvement of the cervix, adnexa, surrounding structures, and lymph nodes, as well as the patient's age, was noted in the pathological report. All patients were divided according to when their operation was done regarding the COVID-19 pandemic.

3.2. METHODS

The data for this thesis included all female patients who underwent surgery in the timeframe from January 2018 until March 2024, after a diagnosis of EC was established. The material resected in surgery was examined at the Pathology Department, pathology report was made and stored in the data base. These reports were used to collect data for this thesis, including tumor staging, histological type, location and size of the tumor, spread to surrounding structures, and patient age.

3.3. STATISTICAL ANALYSIS

Excel tables were used for obtained data input. Statistical data processing was done by MedCalc Statistical Software, Version 19.1.2 (MedCalc Software, Ostend, Belgium; medcalc.org; 2019). The ANOVA, Chi-Squared test and Spearman correlation test were used. The statistical significance was set as $P<0.05$.

3.2.2 ETHICS APPROVAL

The study was approved by the Hospital Ethics Committee of the University Hospital of Split, Croatia under the reference number 2181-147-01-06/LJ.Z.-24-02. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

4. RESULTS

The study included 218 patients with a diagnosis of endometrial cancer who were operated on at the Gynecology Department of the University Hospital of Split and whose pathohistological diagnosis was made at the Pathology Department of the same hospital in the time from January 2018 to March 2024. The patients were divided into three study groups based on the time of diagnosis in regard to the COVID-19 pandemic: before COVID-19 group (BC group), during COVID-19 group (DC group), and after COVID-19 group (AC group).

The DC group had the lowest number of patients (31.7%) compared to the BC group (33.9%) and the AC group (34.4%), the result was not statistically significant (P=0.867). The mean patient's age in years at the time of diagnosis was 64±10 in the BC group, 63±9 in the DC group, and 67±11 in the AC group, which was statistically significant (P=0.056) (Figure 7).

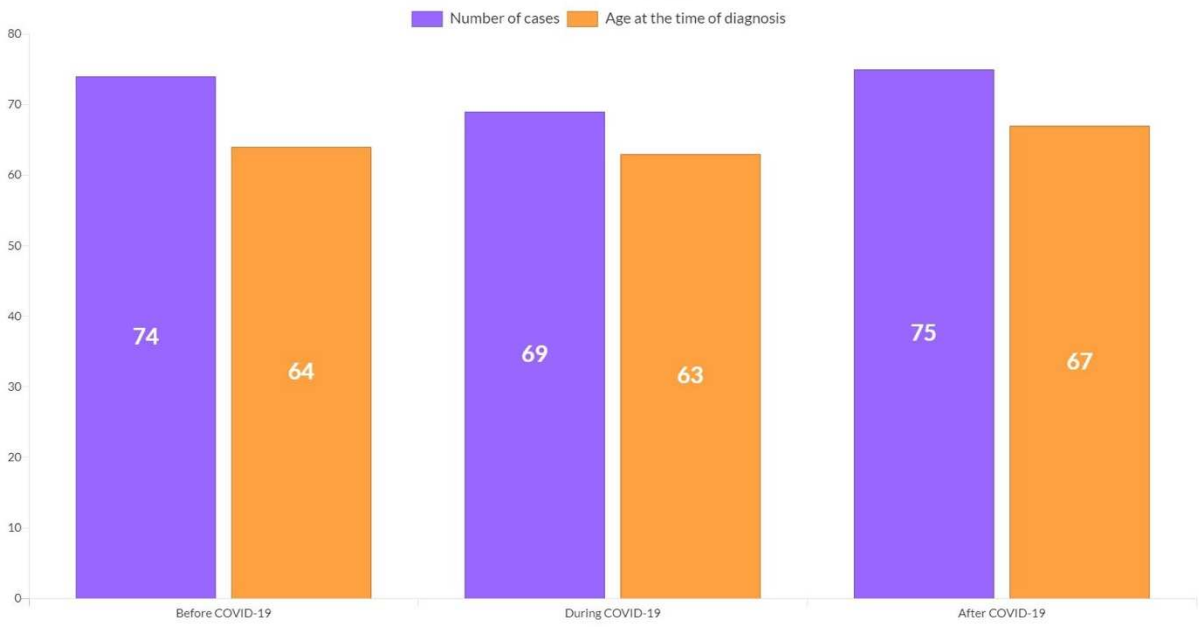

Figure 7. Frequency of endometrial cancer and mean age (years) of the patients at the time of diagnosis in regard to the COVID-19 pandemic.

Table 2. Pathohistological characteristics of endometrial cancers in studied groups

	Before COVID-19 N=74	During COVID-19 N=69	After Covid-19 N=75	P
Tumor size (cm)	3.3 ± 2	3.9 ± 3.9	3.7 ± 2.6	0.856*
Histology type				
EC	62	53	64	
SC	4	6	7	
CC	0	2	2	0.190†
MIXED	8	6	2	
Undifferentiated	0	2	0	
Tumor grade				
Low	50	43	50	
Intermediate	11	8	13	0.542†
High	13	18	12	
Presence of LV	19	14	9	0.102†
Involvement of LUS	3	8	8	0.212†
Involvement of cervix	13	8	14	0.497†
Involvement of other organs	7	4	9	0.434†

The results are presented as mean values ± SD or as absolute numbers, *ANOVA †Chi-square test.
EC=Endometrioid carcinoma, SC=serous carcinoma, CCC=Clear cell carcinoma, LV= lympho-vascular involvement, LUS=lower uterine segment

There was no statistically significant difference in the size of the tumor (P=0.856) between the studied groups. The most common histology type of the tumor was EEC, and the least common was the undifferentiated type in all studied groups, which wasn't statistically significant (P=0.190). As a subtype of EEC, there were four cases with a mucinous differentiation. According to histology grade, the most common grade in all studied groups was low grade, followed by high grade, except in the AC group where the least common grade was the high grade; the findings weren't statistically significant (P=0.542). The presence of lympho-vascular invasion was noted in 19 cases in the BC group, compared to 14 cases in the DC group and 9 in the AC group; the findings weren't statistically significant (P=0.102). There was no statistically significant difference in the involvement of the lower uterine segment (P=0.212) and cervix (P=0.497) by the tumor between the studied groups. Likewise, there was no statistically significant difference in the spread of the tumor to other organs and tissues between the studied groups (P=0.434) (Table 2).

According to World Health Organization pTNM Pathological classification, the highest number of endometrial carcinomas in all studied groups was diagnosed at pT1a stage, which refers to tumor limited to endometrium or invading less than half of myometrium, while the lowest number of cases for all studied groups included categories referring to the spread of the tumor to vagina and parametria (pT3b), lymph node metastasis (pT3aN1 and pT3bN1) and involvement of bladder and/or rectal mucosa (pT4). There was a trend of increase in the number of endometrial cancer cases diagnosed in the pT2 category in the AC group compared to the BC group and DC group. It is to be noted there are more categories in the pTNM classification, but the evaluated patients only presented with these. The presented findings weren't statistically significant (P=0.462) (Table 3).

According to 2023 The International Federation of Gynecology and Obstetrics (FIGO) Classification of cancer of the endometrium, the highest number of cases at the time of diagnosis were in the IA2 category, referring to non-aggressive histological types involving less than half of the myometrium with no or focal lymphovascular involvement, and the lowest number of cases were in categories referring to tumor spread outside of the uterus (IIIA2 and IIIB1) lymph node metastasis (IIIC1) or involvement of bladder and/or intestinal mucosa and/or distant metastasis in all studied groups (IV). Like the pTNM classification, the FIGO classification also had an increase in the IB category, referring to the involvement of more than half of myometrium by non-aggressive histological type in the AC group compared to the BC and the DC group. It is to be noted that there are more categories in the FIGO classification, but the evaluated patients only presented with these. None of the presented findings were statistically significant (P=0.093) (Table 4).

Table 3. Stage of the disease in the studied groups according to World Health Organization pTNM Pathological classification

	Before COVID-19 N=74	During COVID-19 N=69	After Covid-19 N=75	P
Tumor limited to endometrium or invading less than half of myometrium (pT1a)	53	47	43	
Tumor invades one half or more of myometrium (pT1b)	10	12	20	
Tumor invades cervical stroma, but does not extend beyond the uterus (pT2)	8	6	5	
Tumor invades the serosa of the corpus uteri or adnexa (pT3a)	3	2	5	0.462†
Vaginal or parametrial involvement (pT3b)	0	0	1	
Tumor invades the serosa of the corpus uteri or adnexa with pelvic lymph node metastasis (pT3aN1)	0	1	0	
Vaginal or parametrial involvement with lymph node metastasis (pT3bN1)	0	0	1	
Tumor involves bowel/bladder mucosa (pT4)	0	1	0	

The results are presented as mean values ± SD or as absolute numbers, †Chi-square test

Table 4. Stage of the disease in the studied groups according to 2023 The International Federation of Gynecology and Obstetrics (FIGO) Classification

	Before COVID-19 N=74	During COVID-19 N=69	After Covid-19 N=75	P
Non-aggressive histological types involving less than half of the myometrium with no or focal LV involvement (IA2)	50	42	41	
Non-aggressive histological types invading half or more of myometrium with no or focal LV involvement (IB)	9	11	19	
Invasion of cervical stroma of non-aggressive histological type (IIA)	6	2	4	0.093†
Aggressive histological types with any myometrial involvement (IIC)	6	9	4	
Invasion of uterine serosa, adnexa or both (IIIA2)	3	2	5	
Vaginal or parametrial involvement (IIIB1)	0	0	1	
Pelvic lymph node metastasis (IIIC1)	0	1	1	
Tumor involves bowel/bladder mucosa or distant metastasis (IV)	0	1	0	

†Chi-square test

In all studied groups, there was a positive statistical correlation between the histology type of the tumor and both pTNM and FIGO classification of the disease stage. The Spearman correlation for histology type and pTNM disease stage for the BC group was r=0.303 (P=0.008), for the DC group r=0.369 (P=0.002), and the AC group r=0.372 (P=0.001).

The Spearman correlation for histology type and FIGO disease stage for the BC group was r=0.698 (P<0.001), for the DC group r=0.530 (P<0.001), and for the AC group r=0.357 (P=0.002).

5. DISCUSSION

Endometrial carcinoma is the most common gynecological cancer (5). It is associated with various risk factors (6,13,14) and can present with diverse histological patterns (4).

During the COVID-19 pandemic, the world was in a unique state. Secondary to the healthcare danger directly associated with the virus was an increase in the need for healthcare workers to care for all patients, both those infected with the virus and those suffering from other diseases, especially patients who have cancer.

This thesis aims to evaluate if there is a difference between the incidence of ECs diagnosed before, during, and after the COVID-19 pandemic. Due to the restrictions connected to hospital stays and visits, it was expected that patients had limited access to health care and could not reach out for diagnosis and treatment. Additionally, there is no question that hospitals were at their limits with most of their resources and confronted with challenges daily. Whether hospitals could provide every patient with enough appointments and time to establish diagnoses and present treatment options is in question. Consequently, for EC in the University Hospital of Split, fewer patients were expected to have undergone surgery, and the tumor size and stage were suspected to rise after the pandemic and the most intense time of restrictions was over.

According to the results obtained in this study, there was no significant difference in age of the participants before, during, or after the pandemic. There was slight decline in EC cases diagnosed in the DC group of patients and slight increase in the AC group, however the finding wasn't statistically significant. In general EEC makes up the majority of uterine corpus malignancies with 80% in Europe and 70-80% worldwide (4,26), which is in accordance with the results of this study, where EEC presented as the most common as well. There is no significant difference in the tumor size and grade in the timeframe from this study. As stated in the results for the pTNM classification, the most common stage was pT1a, which showed no rise after the pandemic. According to the FIGO classification, the most common stage was IA2, known as non-aggressive. Serous, clear cell and mixed endometrial carcinoma, were the least common histological types in all studied groups, although overall there were differences between groups, the results were statistically insignificant.

According to literature, the importance of early screening and diagnostic delay played a role in establishing uninterrupted clinical activity (27). Not only in adults, but also in children the incidence of new cancer diagnoses had no significant rise during the COVID-19 pandemic (28).

Concluding from our results, the University Hospital of Split was able to take care of their patients with EC at the same level during the whole time between January 2018 and March 2024. There was no difference for patients, and their diagnosis and treatment were dealt with as before and after the COVID-19 pandemic.

Since this is a retrospective study and the fact that reports from only one clinical center were used limits the significance of the results. Additionally, only patients who had been treated surgically were selected to participate. Patients treated otherwise, for example, by curettage, were excluded since their material could not be sufficiently examined.

6. CONCLUSION

1. There was no significant statistical difference in the incidence of EC operated and diagnosed in University Hospital of Split before, during, and after the COVID-19 pandemic.
2. There was no significant statistical difference in gross and histological characteristics of EC between the three studied groups in regard to the time of the COVID-19 pandemic.
3. The was no significant statistical difference in the stage of the disease at the time of diagnosis, between the three studied groups according to pTNM stage by the World Health Organization classification of female genital tumors, as well as according to FIGO classification.

Further studies are needed to elaborate on this topic. More clinical centers could be included, and different diseases could be investigated for comparisons. It would be interesting to see if these results are specific only for this study or are constant for the same center and different diseases or another center and EC.

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8. SUMMARY

Objectives: This study aimed to evaluate the incidence of EC in the University Hospital of Split before, during, and after the COVID-19 pandemic. It aimed for the gross and histological characteristics to be investigated for comparison between the three study groups, and for the stage of disease at the time of diagnosis to be determined.

Patients and methods: This study was designed as a retrospective study. The dataset involves 218 female patients who underwent surgery for EC between January 2018 and March 2024. The pathology reports are evaluated, and data is collected to compare between three study groups according to the COVID-19 pandemic.

Results: The patients included in this study were divided into three groups, before COVID-19 (BC), during COVID-19 (DC), and after COVID-19 (AC). The mean patient age in years at the time of diagnosis was 64±10 in the BC group, 63±9 in the DC group, and 67±11 in the AC group. Between the studied groups, there was no significant difference in the size of the tumors (P=0,856). The least common type diagnosed was UC, and the most common type was EEC in all studied groups. Low grade was the most common histological grade. For lympho-vascular invasion, 19 cases were noted in the BC group, 14 cases in the DC group, and nine cases in the Ac group. The involvement of the lower uterine segment (P=0,212) and cervix (P=0,497), was of no difference in each of the groups. Similarly, for the spread to other organs and tissues there was no significant difference. According to the World Health Organization pTNM Pathology classification and to the 2023 FIGO classification. most of the ECs were at pT1a stage and IA2 category. None of the results were statistically significant. The Spearman correlation for histology type and pTNM disease stage for the BC group was r=0,303 (P=0,008), for the DC group r=0,369 (P=0,002), and the AC group r=0,372 (P=0,001). The Spearman correlation for histology type and FIGO disease stage for the BC group was r=0,698 (P<0,001), for the DC group r=0,530 (P<0,001), and for the AC group r=0,357 (P=0,002).

Conclusion: The findings from this study demonstrate that the University Hospital of Split was able to provide sufficient care for their patients diagnosed with EC, even during a global pandemic. There was no significant difference between the study groups, which shows that surgery was performed in a timely manner and in the same amount at all times. Tumor grade and size showed no significant increase or decrease during or after the pandemic, which also underlined the timely intervention and care for patients.

9. CROATIAN SUMMARY

Naslov: Pojavnost karcinoma endometrija dijagnosticiranih u KBC-u Split u razdoblju prije, za vrijeme, i nakon COVID-19 pandemije

Ciljevi: Ovo istraživanje imalo je za cilj procijeniti incidenciju EC-a u KBC-u Split prije, tijekom i nakon pandemije COVID-19. Cilj je bio istražiti grube i histološke karakteristike za usporedbu između tri ispitivane skupine, te odrediti stadij bolesti u vrijeme dijagnoze.

Ispitanici i metode: Ova je studija osmišljena kao retrospektivna studija. Skup podataka uključuje 218 pacijentica koje su bile podvrgnute kirurškom zahvatu zbog EC-a između siječnja 2018. i ožujka 2024. Patološka izvješća se procjenjuju, a podaci prikupljaju kako bi se usporedile tri skupine prema pandemiji COVID-19.

Rezultati: Pacijenti uključeni u ovu studiju podijeljeni su u tri skupine, prije COVID-19 (BC), tijekom COVID-19 (DC) i nakon COVID-19 (AC). Prosječna dob bolesnika u godinama u vrijeme postavljanja dijagnoze bila je 64±10 u skupini BC, 63±9 u skupini DC i 67±11 u skupini AC. Između ispitivanih skupina nije bilo značajne razlike u veličini tumora (P=0.856). Najrjeđe dijagnosticiran tip bio je UC, a najčešći tip EEC u svim ispitivanim skupinama. Niski stupanj bio je najčešći histološki stupanj. Za limfo-vaskularnu invaziju zabilježeno je 19 slučajeva u skupini BC, 14 slučajeva u skupini DC i devet slučajeva u skupini Ac. Zahvaćenost donjeg uterinog segmenta (P=0.212) i cerviksa (P=0.497) nije se razlikovala u svakoj od skupina. Slično, za širenje na druge organe i tkiva nije bilo značajne razlike. Prema klasifikaciji pTNM patologije Svjetske zdravstvene organizacije i klasifikaciji FIGO iz 2023. većina EC-a bila je u stadiju pT1a i kategoriji IA2. Nijedan od rezultata nije bio statistički značajan. Spearmanova korelacija za histološki tip i pTNM stadij bolesti za skupinu BC bila je r=0.303 (P=0.008), za skupinu DC r=0.369 (P=0.002), a skupinu AC r=0.372 (P=0.001). Spearmanova korelacija za histološki tip i stadij FIGO bolesti za BC skupinu bila je r=0,698 (P<0.001), za DC skupinu r=0,530 (P<0.001), a za AC skupinu r=0,357 (P=0.002).

Zaključci: Nalazi ovog istraživanja pokazuju da je KBC Split uspio pružiti adekvatnu skrb svojim pacijentima s dijagnozom EC-a, čak i tijekom globalne pandemije. Nije bilo značajne razlike između ispitivanih skupina, što pokazuje da je kirurški zahvat obavljen pravodobno i u cijelom vremenu u jednakoj količini. Gradus i veličina tumora nisu pokazali značajno povećanje ili smanjenje tijekom ili nakon pandemije, što je također naglasilo pravovremenu intervenciju i skrb za pacijente.