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Original Article

Characteristics and patterns of care of endometrial cancer before and during COVID-19 pandemic

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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) outbreak has correlated with the disruption of screening activities and diagnostic assessments. Endometrial cancer (EC) is one of the most common gynecological malignancies and it is often detected at an early stage, because it frequently produces symptoms. Here, we aim to investigate the impact of COVID-19 outbreak on patterns of presentation and treatment of EC patients.
Methods: This is a retrospective study involving 54 centers in Italy. We evaluated patterns of presentation and treatment of EC patients before (period 1: March 1, 2019 to February 29, 2020) and during (period 2: April 1, 2020 to March 31, 2021) the COVID-19 outbreak.
Results: Medical records of 5,164 EC patients have been retrieved: 2,718 and 2,446 women treated in period 1 and period 2, respectively. Surgery was the mainstay of treatment in both periods (p=0.356). Nodal assessment was omitted in 689 (27.3%) and 484 (21.2%) patients treated in period 1 and 2, respectively (p<0.001). While, the prevalence of patients undergoing sentinel node mapping (with or without backup lymphadenectomy) has increased during the COVID-19 pandemic (46.7% in period 1 vs. 52.8% in period 2; p<0.001). Overall, 1,280 (50.4%) and 1,021 (44.7%) patients had no adjuvant therapy in period 1 and 2, respectively (p<0.001). Adjuvant therapy use has increased during COVID-19 pandemic (p<0.001).
Conclusion: Our data suggest that the COVID-19 pandemic had a significant impact on the characteristics and patterns of care of EC patients. These findings highlight the need to implement healthcare services during the pandemic.

Keywords: Endometrial Cancer; COVID-19; Uterine cancer; SARS-CoV-2

Synopsis
The prevalence of patients with early-stage endometrial cancer (EC) has been lower during coronavirus disease 2019 (COVID-19) pandemic than before its onset. Further evidence is needed to assess the impact of COVID-19 pandemic on survival outcomes of EC patients.

INTRODUCTION

Endometrial cancer (EC) is one of the most common gynecological cancers in developed countries [1]. It is estimated that more than 55,000 new EC cases are diagnosed every year in the United States [1]. Over the last decade, the incidence of EC has increased by more than 20,000 cases/year [2]. Similarly, the incidence of EC in Europe is increasing due to the aging of populations and increased prevalence of obesity [3]. Generally, EC is considered a disease with good prognosis, since the majority of patients are diagnosed at early stage of disease. The main reason for this is that EC frequently produces symptoms, namely abnormal vaginal bleeding. Although no screening activities are approved for early detection of EC, regular visits and prompt assessments in patients with new-onset symptoms have been useful in improving early detection of uterine malignancies [4].

Over the last year, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) respiratory disease (coronavirus disease 2019, COVID-19) has been spreading worldwide, dramatically changing everyday life. On February 3, 2020, the World Health Organization (WHO) proposed the '2019 COVID-19 Strategic Preparedness and Response Plan,' which includes accelerating research and development processes as one of the main strategies against the

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COVID-19 outbreak. On March 11, 2020, the WHO declared COVID-19 a pandemic [5]. Italy was the first European country suffering the spread of COVID-19. In order to flatten the growth curve and to face the growing need for assistance of COVID-19 patients, physicians have started delaying non-urgent procedures. This has partly translated in the risk of diagnosis and treatment procrastination, with significant negative impacts on the outcomes of patients with cancer. Indeed, COVID-19 pandemic has negatively influenced the timing of screening activities and regular periodic visits [6]. Disruption of screening activities, periodic visits, and diagnostic assessments have delayed regular medical investigations [6-9]. This is of paramount importance in subjects at risk, and especially to those patients who developed new symptoms and need to be investigated in the suspect of cancer diagnosis. To date, several opinions and surveys have been published on this topic [5,10,11]. Emerging data suggest that the COVID-19 outbreak might influence patterns of disease presentation, compromising the possibility of early access to care for patients with malignancies [6-10]. However, so far, no studies specifically evaluated the real impact of COVID-19 on the attitudes, practice, and the workflow in the setting of oncology. We evaluated patterns of presentation and treatment of EC patients before and during the COVID-19 pandemic. EC represents an ideal target to assess the impact of COVID-19 for three main reasons: i) it is a common gynecological occurrence; ii) it is generally detected at an early stage of disease; and iii) it is usually related to favorable oncologic outcomes. Hence, we performed a large multi-institutional study evaluating the COVID-19 pandemic on patients diagnosed with EC, with the aim to verify whether diagnostic and treatment's attitudes have changed across these 2 periods.

MATERIALS AND METHODS

1. Methods

This is a multi-institutional retrospective study coordinated by the Fondazione IRCCS Istituto Nazionale dei Tumori. As coordinator center the Institutional Review Board of the Fondazione IRCCS Istituto Nazionale dei Tumori approved this investigation (#62/20). For the present study, we collected medical records of consecutive patients with newly diagnosed EC treated in Italy before (period 1: from March 1, 2019 to February 29, 2020) and during (period 2: from April 1, 2020 to March 31, 2021) the COVID-19 outbreak. This study involved 54 high-volume centers in Italy. We collected data from any regional referral centers or cancer centers in Italy. **Table S1** displays the centers participating in the study.

The primary endpoint measures were: i) the prevalence of patients affected by International Federation of Obstetrics and Gynecologists (FIGO) stage >I disease at presentation; ii) the prevalence of adjuvant therapy indication in the 2 periods. As secondary endpoints, we sought to report changes in EC management during the COVID-19 outbreak. We included consecutive patients receiving treatment (i.e., surgery, radiotherapy, and/or anticancer systemic treatment) in period 1 and 2. To minimize possible biases we decided to exclude cases treated in March 2020, focusing only on cases treated before and during the COVID-19 outbreak. In March 2020 only few regions in the North of Italy were affected by the pandemic. Since April 2020, the whole Italian healthcare care system was impacted by COVID-19 [12]. We included all patients aged ≥18 years old, with a confirmed histological diagnosis of EC, regardless of the type of treatment. In all included centers, data concerning surgical procedures, peri-operative details, adjuvant therapy, as well as follow-up evaluations were recorded in computerized databases, updated by trained residents and nurses on a regular basis. The taxonomy proposed by the WHO was used to designate EC histological

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Conflict of Interest
The first author is a principal editor of the Journal of Gynecologic Oncology. No other potential conflict of interest relevant to this article was reported

subtypes [13,14]. The degree of glandular differentiation and cytologic atypia to determine architectural grade and stage were reported according to the FIGO criteria [13,14]. Details about surgical techniques, adjuvant therapies, and follow-up schedules are reported elsewhere [15-18]. During the two study periods, there were no significant differences in the facilities available for patients care and in the referral patterns of our service. Other features of patient management remained consistent in the two periods.

2. Statistical methods

Basic descriptive statistics were used to describe the study populations. Differences in categorical variables were analyzed using the Fisher exact and χ^2 test when comparing 2 and 3 (or more) groups, respectively. When indicated odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. Student's t-test and Mann-Whitney test were used to compare continuous variables as appropriate. The p-values <0.05 were considered statistically significant. Statistical analysis was performed with GraphPad Prism version 6.0 (GraphPad Software, San Diego CA, USA) and IBM-Microsoft SPSS version 20.0 (IBM Corp., Armonk, NY, USA) for Mac.

RESULTS

Charts of 5,164 EC patients were retrieved from 54 Italian centers over the whole study period. Overall, 2,718 and 2,446 women with EC received treatment in period 1 and 2, respectively. **Table 1** shows the main characteristics of the study population in the 2 time periods. The prevalence of patients aged > 65 years was similar between the 2 study periods (1,400 [51.5%] in period 1 vs. 1,248 [51.0%]; p=0.726). Similarly, the prevalence of elderly patients (i.e., aged >85 years) was comparable between groups (189 [6.9%] vs. 180 [7.4%]; p=0.572).

Considering data on the histological characterization, the prevalence of endometrioid FIGO grade 1, 2, and 3 was consistent over the study period (p=0.855). However, the prevalence

Table 1. Characteristics of EC patients included in the study

Characteristics	Period*		p-value
	Period 1	Period 2	
No. of cases	2,718	2,446	-
Age of patients (yr)			0.742
<50	306 (11.3)	262 (10.7)	-
50–64	1,012 (37.2)	936 (38.2)	-
65–84	1,211 (44.6)	1,068 (43.7)	-
>84	189 (6.9)	180 (7.4)	-
Histology			0.178
Endometrioid FIGO G1	808 (29.7)	719 (29.3)	-
Endometrioid FIGO G2	1,019 (37.5)	878 (35.9)	-
Endometrioid FIGO G3	447 (16.4)	400 (16.4)	-
Non-endometrioid	425 (15.6)	438 (17.9)	-
Unknown	19 (0.7)	11 (0.5)	-
FIGO stage			0.003
Stage I	2,021 (74.3)	1,754 (71.7)	-
Stage II	179 (6.6)	176 (7.2)	-
Stage III	348 (12.8)	349 (14.3)	-
Stage IV	129 (4.7)	167 (6.8)	-

Data are reported in number (%).
EC, endometrial cancer; COVID-19, coronavirus disease 2019; FIGO, International Federation of Obstetrics and Gynecologists.
*This study has evaluated patterns of presentation and treatment of EC patients before (period 1: March 1, 2019 to February 29, 2020) and during (period 2: April 1, 2020 to March 31, 2021) the COVID-19 outbreak.

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Table 2. Details of treatment modalities adopted for managing EC before and during COVID-19 pandemic

Variables	Period*		p-value
	Period 1	Period 2	
No. of cases	2,718	2,446	-
Primary treatment			0.361
Surgery	2,539 (93.4)	2,286 (93.5)	-
Other therapies	169 (6.2)	156 (6.4)	-
No treatment/palliation	10 (0.4)	4 (0.2)	-
Other non-surgical treatments			0.048
Radiotherapy	24 (0.9)	21 (0.9)	-
Chemotherapy	29 (1.1)	49 (2.0)	-
Radio + chemotherapy	25 (0.9)	16 (0.7)	-
Hormonal therapy	19 (0.7)	14 (0.6)	-
IUD/hysteroscopic resection	72 (2.6)	56 (2.3)	-
Type of surgery†			0.096
Laparoscopy	1,400 (55.1)	1,273 (55.7)	-
Robotic assisted	448 (17.6)	390 (17.1)	-
Open surgery	666 (26.2)	582 (25.5)	-
Vaginal	25 (0.9)	41 (1.7)	-
Waiting time between diagnosis and surgery (days)†	25 (7–41)	23 (6–53)	0.654
Type of nodal assessment at surgery†			<0.001
Sentinel node mapping	961 (37.8)	973 (42.5)	-
Sentinel node mapping + lymphadenectomy	224 (8.9)	234 (10.2)	-
Pelvic Lymphadenectomy	456 (17.9)	422 (18.5)	-
Pelvic + para-aortic lymphadenectomy	206 (8.1)	173 (7.6)	-
None	692 (27.3)	484 (21.2)	-

Data are reported in number (%), or median (range).
EC, endometrial cancer; COVID-19, coronavirus disease 2019; IUD, intra-uterine devices
*This study has evaluated patterns of presentation and treatment of EC patients before (period 1: March 1, 2019 to February 29, 2020) and during (period 2: April 1, 2020 to March 31, 2021) the COVID-19 outbreak; †This analysis is restricted only to patients having surgery.

of non-endometrioid EC was lower in period 1 than in period 2 (15.6% vs. 17.9%; p=0.032). **Table 2** reports details on the treatment of patients in the 2 study periods. Surgery was the mainstay of treatment before and during the COVID-19 pandemic. Overall, 2,539 and 2,286 women received surgery in period 1 and 2, respectively (93.4% vs. 93.5%; p=0.948). Primary conservative attempts (i.e., progesterone-based therapy) was performed in 72 (2.7%) and 56 (2.3%) patients in period 1 and 2, respectively (p=0.406).

The adoption of minimally invasive surgery was consistent in the two study periods (p=0.976). Before COVID-19 pandemic, 1,848 (72.8%), 666 (26.3%), and 25 (0.9%) patients had minimally invasive, open and vaginal surgery, respectively. During the COVID-19 pandemic, 1,663 (72.8%), 582 (25.5%), and 41 (1.7%) patients had minimally invasive, open, and vaginal surgery, respectively. Restricting the analysis to patients treated with surgery, we observed that sentinel node mapping was the most adopted method before and during the COVID-19 pandemic. Before the COVID-19 pandemic, sentinel node mapping, sentinel node mapping plus backup lymphadenectomy, and lymphadenectomy (pelvic and/or para-aortic) were performed in 961 (37.0%), 224 (8.9%), and 662 (26.0%) patients, respectively. During the COVID-19 pandemic, sentinel node mapping, sentinel node mapping plus backup lymphadenectomy, and lymphadenectomy (pelvic and/or para-aortic) were performed in 973 (42.5%), 234 (10.2%), and 595 (26.1%) patients, respectively. Nodal disease assessment was omitted in 692 (27.3%) and 484 (21.2%) patients treated in periods 1 and 2, respectively (p<0.001). Conversely, the prevalence of patients undergoing sentinel node mapping (with or without backup lymphadenectomy) has increased during the COVID-19 pandemic (46.7% in period 1 vs. 52.8% in period 2; p<0.001).

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Table 3. Details of treatment modalities adopted for managing EC before and during COVID-19 pandemic

Variables	Period*		p-value
	Period 1	Period 2	
No. of patients having surgery	2,539	2,286	-
Adjuvant therapy†			<0.001
Yes	1,259 (49.6)	1,265 (55.3)	-
No	1,280 (50.4)	1,021 (44.7)	-
Type of adjuvant therapy‡			0.064
Vaginal brachytherapy (VB)	304 (11.9)	253 (11.1)	-
External radiotherapy (+/−VB)	317 (12.5)	323 (14.1)	-
Chemotherapy (+/−VB)	274 (10.8)	310 (13.5)	-
Chemo-radiotherapy	364 (14.3)	379 (16.6)	-

Data are reported in number (%).
EC, endometrial cancer; COVID-19, coronavirus disease 2019; VB, vaginal brachytherapy.
*This study has evaluated patterns of presentation and treatment of EC patients before (period 1: March 1, 2019 to February 29, 2020) and during (period 2: April 1, 2020 to March 31, 2021) the COVID-19 outbreak; †This analysis is restricted only to patients having surgery; ‡This analysis is restricted only to patients having surgery plus adjuvant therapy.

Table 3 shows the details of adjuvant treatment used in the study population, before and during COVID-19 pandemic. Overall, 1,280 (50.4%) and 1,021 (44.7%) patients had no adjuvant therapy in period 1 and 2, respectively (p<0.001). The adoption of vaginal brachytherapy as adjuvant treatment remained stable in the study periods (11.9% vs. 11.1%; p=0.325). Adjuvant therapies indication has increased during the COVID-19 pandemic (p<0.001). In particular, the use of adjuvant radiotherapy (26.8% vs. 30.7%; p=0.001) and chemotherapy (25.1% vs. 30.1%; p<0.001) alone or in combination increased from period 1 to 2.

DISCUSSION

The present study investigated the characteristics and patterns of care of patients diagnosed with EC, before and during the COVID-19 pandemic. This large retrospective analysis reported several noteworthy findings. First, we observed that during the COVID-19 pandemic patients were more likely to be treated for advanced-stage disease (FIGO stage >I, with a high rate of patients with FIGO stage III–IV disease). Second, there was a higher proportion of patients treated with adjuvant therapy among those treated with surgery during the COVID-19 pandemic, as compared with those undergoing surgery before the pandemic. Third, the number of EC patients treated per year has decreased during the COVID-19 pandemic.

Generally, EC is an indolent entity. The short-term time interval, starting from the onset of the pandemic, it is not fully explaining the high prevalence of advanced disease observed during COVID-19 pandemic than before. Possibly, we can suppose that is not the high incidence of advanced disease, but the low prevalence of early-stage disease during the pandemic that is driving these findings. Hence, the “real” high prevalence of advanced disease could be expected in the next years. COVID-19 has posed a significant challenge to worldwide health care systems. One of the main indirect consequences of COVID-19 pandemic lies in the limited access to health care services. Reluctance to report symptoms, potentially owing to fear of COVID-19, might become one of the main drivers of lower detection rates of early-stage EC. As aforementioned, the COVID-19 outbreak has correlated with the disruption of screening activities, regular follow up visits, and diagnostic assessments [6-10]. Many patients are delaying or missing their visits, even in presence of symptoms. However, to date the impact of COVID-19 on patients with newly diagnosed cancer is unclear. In the present paper, we decided to focus on the impact of COVID-19 in

EC patients. EC is often diagnosed in the early phase of the disease (FIGO stage I) and it is often characterized by a good prognosis. In our study, we observed that during the COVID-19 pandemic patients were more likely to be diagnosed with more advanced disease, as compared with the period before the pandemic. Similarly, the need for adjuvant treatments was higher during COVID-19 pandemic than before, while the prevalence of patients receiving non-surgical treatments remained steadily stable over time. Delayed diagnosis might potentially explain our results. Unexpectedly, the crude number of EC cases receiving medical and/or surgical treatment has decreased during the pandemic. Of note, we are missing several patients with early-stage disease. Few features might explain these findings: i) the number of patients treated in the two periods reflects a physiological variation of EC incidence over time ii) patients with more favorable disease are treated in more peripherical centers (e.g., low volume hospitals), thus meaning there might have been an allocation bias; iii) some patients with clinical stage I disease might be treated with intra-uterine devices (IUD) by general practitioners and not referred to the hospitals; and iv) patients are not diagnosed with EC since they are missing their visits. The reason is likely related with a multi-factorial process. Further evidence will be necessary to assess the characteristics and patterns of presentation of EC patients during the next years. We are expecting that our results would be more evident in the next future, however with a potential opposite trend due to the implementation of COVID-19 vaccination among patients with cancer.

Interestingly, an Israeli Gynecologic Oncology Group retrospective study evaluated the role of EC diagnosis in asymptomatic patients [19]. The Authors compared data of 1,374 patients presenting with postmenopausal bleeding with 233 asymptomatic patients (diagnosed with EC after instrumental finding of thickened endometrium or polyps). Although the authors observed that EC diagnosed in asymptomatic postmenopausal patients is not associated with a survival advantage, the prevalence of patients diagnosed with more advanced disease stages and adjuvant therapy administration rate is lower in asymptomatic patients [19]. These findings seem to corroborate and partially explain our results.

Six points of the present investigation deserve to be addressed: i) Due to the absence of follow-up, we are not able to evaluate the impact of the COVID-19 pandemic on the oncologic outcomes of EC patients involved in this study. ii) We arbitrarily decided to omit data of March 2020 from the analysis, due to the limited impact of COVID-19 in that period (i.e., only few regions in the North of Italy were affected by the pandemic by March 2020) [5,12]. iii) We collected a huge amount of data (more than 5,000 patients) from the whole Italian territory, with a potential missing of EC cases diagnosed and treated in low volume centers. iv) Data about the prevalence of COVID-19 infections in EC patients (before or after treatments) is lacking. However, the main outcome measure of this research was not to assess the impact of COVID-19 disease on patients, but to assess how the COVID-19 outbreak impacted on patients' access to care. v) Data about the time between symptom presentation and date of a check-up at hospital, and the time between first histological diagnosis and date of surgery are important variables impacting outcomes. Further studies have to assess how waiting time impacted on survival outcomes, according to various histological features. vi) In Italy, the vaccination campaign against COVID-19 was managed by the Ministry of Health and (for patients) started on March 1, 2021. Hence, our data are reflecting the pre-vaccination era. We can speculate that the implementation of vaccination might improve the patients' access to care.

The inherent biases related to the retrospective nature of the study design are the main weaknesses of the present paper. Additionally, selection biases might impact the

interpretation of our results. Possibly, advanced and more challenging cases are more likely to be referred to high-volume centers, while peripheral centers are more likely to treat more simple cases. However, if this is true this evidence should have been detected even in the pre-pandemic period. The main strengths of this paper consist in: i) the large series of patients enrolled in this study and ii) the strong collaboration among a high number gynecological centers in Italy, suggesting the proactive and cooperative approach to the actual COVID-19 pandemic. Interestingly, about 8,000 new EC cases are diagnosed every year in Italy [20]. Hence, our study collected data about one third of EC patients having diagnosis and treatment in Italy in the last 2 years.

In conclusion, our study shows that the characteristics and patterns of care are changing during the COVID-19 pandemic. Compared with the pre-pandemic period, patients are more likely diagnosed with advanced stage disease (FIGO stage >I) during COVID-19 pandemic, with a consequently higher indication for adjuvant therapies. Due to the absence of mature post-treatment data, the impact of COVID-19 on survival outcomes of EC cannot be assessed yet. However, we have to highlight that possible physiological variations in pattern of EC presentation and allocation biases are influencing these results. Additionally, we have to point out that the modifications in EC presentation pattern presentation are minimal and not clinically meaningful. Owing to the indolent nature of EC we are not expected that delaying primary treatment of few months correlated with a high proportion of advanced stage of disease. Possibly, the number of patients with advanced stage is less diluted due to the decrease of number of patients with early-stage disease. Further analysis of our collaborative dataset will clarify these features in the next future. Similarly, further prospective evidence is necessary to corroborate our preliminary results. Attempts are warranted to improve risk-based strategies to recover, preserve, and implement healthcare services during the COVID-19 pandemic.

SUPPLEMENTARY MATERIAL

Table S1
Centers participating in this study

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