European Journal of Obstetrics & Gynecology and Reproductive Biology 242 (2019) 36–42

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Management of endometrial cancer in patients aged 80 years and older Identifying patients who may benefit from a curative treatment

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ARTICLE INFO

Article history:
Received 15 March 2019
Received in revised form 8 September 2019
Accepted 14 September 2019

Keywords:
Endometrial cancer
Elderly
Cancer-specific survival

ABSTRACT

Objective: The goal of this study was to evaluate the demographic characteristics, pathology, treatment, prognostic factors and survival rates in elderly patients with endometrial cancer, and to compare their results with those of younger ones, in order to define the specific characteristics of this malignancy in this population.

Study design: Retrospective analysis of all endometrial cancer patients managed at the University Hospital of the Canary Islands (Spain) between 1990 and 2016. Survival curves were calculated by using the Kaplan-Meier method and compared with the log-rank test. Logistic regression analysis was used to assess the independent effect of different variables on cancer-specific survival. Statistical significance was considered for $p < 0.05$.

Results: The study included 1799 endometrial cancer patients; 170 of them (9.4%) were 80 years old or older. Elderly patients received less surgery (68.2% vs. 92.4%), lymphadenectomy (10.3% vs. 26.2%) and adjuvant treatment (37.1% vs. 51.2%) than younger ones, and presented higher probability of receiving palliative treatment (27.6% vs. 4%). Endometrioid tumors were more frequently diagnosed in younger patients (78.8% vs. 62.9%), while type 2-endometrial cancer was more frequently diagnosed in elderly ones (37.1% vs. 21.2%).

Cancer-specific survival in older patients was significantly poorer than in younger ones, with a mean of 61.4 months (95%CI 51.7–71.1) versus 226 months (95%CI 218.9–233.1), respectively. In a multivariate analysis: age, FIGO stage, histology, tumor differentiation and adjuvant treatment were independently associated with survival.

Conclusion: Although endometrial cancer is more aggressive in older patients, they are less likely to receive optimal treatment, which negatively affects their survival. Specific guidelines for the management of this population, including a comprehensive geriatric assessment, should be developed to improve their prognosis.

Introduction

Endometrial cancer (EC) is the most common pelvic gynecological tumor in European women, and the fourth most common cancer, after breast, colorectal and lung. During the last 30 years, the incidence of EC has gradually increased (1% annually), consequently increasing its associated mortality [1]. Advanced age is currently considered a major risk factor for the development of EC, since the frequency of this malignancy is known to increase with population aging. According to different published studies, the mean age at diagnosis is 63 years, and 8–14% patients diagnosed with EC are considered elderly [2,3].

Spain is the European country with the highest life expectancy. Spanish women have the second greatest longevity worldwide, with an estimated life expectancy of 85.6 years, only after Japanese women. Specifically, after reaching the age of 80, the Spanish women can expect to celebrate the 90, since their life expectancy is 11.2 years, which means an increase of 1.7 years in the last decade. Indeed, according to predictions, the largest population growth in Spain will correspond to advanced age groups. In particular, the population over 65 years of age is expected to reach 37% of the total population by 2052 [4]. Similarly, in 2017 octogenarians and older individuals constituted 5.5% of the total European population, and predictions indicate that they will reach 12.1% by 2060 [5].

According to several studies, elderly women with EC are frequently diagnosed at advanced stages of the disease, often with histologically aggressive tumors. Actually, age itself is considered to be a risk factor for poor prognosis, since the biological aggressiveness of tumors seems to increase with age [6,7]. Given

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https://doi.org/10.1016/j.ejogrb.2019.09.007
0301-2115/

that medical comorbidities are more frequent among aged individuals, elderly EC patients may be at risk of receiving insufficient treatment; thus, the management of EC in this population may require a multidisciplinary approach. Moreover, elderly patients are often excluded or underrepresented in clinical trials evaluating the effects of medical treatments of cancer, which limits the applicability of the results.

The goal of study was to evaluate the demographic characteristics, pathology, treatment, prognostic factors and survival rates in a large cohort of elderly EC patients and to compare their results with those of younger ones, in order to define the specific characteristics of this malignancy in this population.

Methods

The study was designed as a retrospective analysis of all EC patients diagnosed and treated at the Department of Gynecology Oncology of the University Hospital of the Canary Islands (Spain) during the 27 year period from January 1990 to December 2016. The gynecological cancer database and the pathology records were reviewed and the following parameters were evaluated for these patients: demographic characteristics, treatment, surgical approach, tumor stage, pathology, adjuvant therapy, relapse and cancer-specific survival. There is no consensus in the current literature on the definition of an elderly person. Different criteria have been proposed: the WHO defines an elderly subject as a person over 65 years; the NCI considers people over 75 years to be elderly; and according to another, socioeconomic criterion, an elderly person is someone who is no longer working [8]. Since this study was focused on extreme population ages, we considered patients over 80 years of age to be elderly patients. Thus, for the purpose of the study, two patient groups were defined: patients of 80 years of age or more and patients below 80 years of age.

Surgery was considered the cornerstone of EC treatment for all patients and consisted of total hysterectomy and bilateral salpingo-oophorectomy. Staging surgery was performed as pelvic/paraaortic lymphadenectomy in type 2-EC and stage $\geq$ IB type 1-EC, according to the surgeon's criterion. In 2007, with the implementation of minimally invasive surgery, the surgical approach to EC patients changed in our centre. Thus, from that year on, patients were treated with laparoscopic surgery, provided that it was not contraindicated. Intraoperative complications included any events occurred during surgery. Surgical postoperative complications were classified according to the modified Clavien-Dindo system; for the purpose of this study grade 3 and 4 complications, occurred within 6 weeks after surgery, were analysed. Pathologist experienced in gynecologic oncology reviewed all tumor slides. Adjuvant treatment was proposed according to the updated scientific evidences available on each period of the study. All cases were managed on a multidisciplinary basis.

EC was staged with the FIGO 2009 staging system. In order to enable adequate comparisons, the staging of tumors managed before 2009 was updated according to the FIGO 2009 classification. Patient follow-up included a control visit every 6 months during the first 5 years and annually afterwards. Cancer specific-survival was the primary endpoint of the study, and was defined as the time in months from the date of the diagnosis to the date of the last visit or disease-related death. The cut-off point for the survival analysis was December 31st, 2016. This study was approved by the local Ethics Committee.

Data were analysed with the SPSS software, version 20.0 (IBM Corp., Armonk, NY). For qualitative variables, absolute and relative frequencies were calculated and compared with the chi-square test or the Fisher's exact test. Quantitative variables were expressed as mean or median and standard deviation and compared with the Student's test or the Mann-Whitney's test. Survival curves were calculated by using the Kaplan-Meier method and compared with the log-rank test. Logistic regression analysis was used to assess the independent effect of different variables on overall survival. Statistical significance was considered for $p < 0.05$.

Results

Between January 1st 1990 and December 31st 2016, a total of 1799 EC patients were managed at the Department of Gynecology Oncology of the University Hospital of the Canary Islands, with a median follow-up period of 62.6 months (range 1–300). A group of 170 patients (9.4% of the study population) were 80 years old or older. The proportion of elderly patients gradually increased between 1990 and 2016, from 3.1% of the annual population to more than 14%.

The median age at diagnosis was 65 years (range, 17–93); the distribution of patients according to age was as follows: 1.8% younger than 40 years [32], 6% between 40–49 (107), 23.8% 50–59 (427), 35.4% 60–69 (636), 23.6% 70–79 (422) and 9.4% 80 years and older (170). In the group of younger patients, the median age at diagnosis was 64 years, while in elderly patients it was 83 years. Younger EC patients showed a tendency to earlier menarche and later menopause, thus consequently, to more years of hormonal endometrial stimulation. Moreover, the proportion of nulliparous women was significantly higher among younger patients than in older ones (19.9% vs. 14.1%). No significant differences were found

Table 1
Clinical characteristics of the studied population (BMI = body mass index).

	≥80 years (n = 170)	<80 years (n = 1629)	All patients (n = 1799)	p
Age (median, range)	83 (80-93)	64 (17–79)	65 (17-93)	<0.0001
Age at menarche (mean, range)	13.1 (8-18)	12.7 (8–25)	12.8 (8-25)	0.02
Age at menopause (mean, range)	50.2 (37-60)	50.7 (30–64)	50.6 (30-64)	0.1
Difference menopause-menarche (mean, range)	37 (22-49)	37.8 (15–52)	37.7 (15-52)	0.06
Menopause status (%, n)	100% (170)	88.8% (1447)	89.8% (1617)	<0.0001
Nulliparity (%, n)	14.1% (24)	19.9% (324)	19.3% (348)	0.01
Number of pregnancies (mean, range)	3.52 (0–15)	3.04 (0–19)	3.08 (0–19)	0.02
ECOG 0 (%, n)	25.3% (43)	79.2% (1291)	68.3% (1334)	<0.0001
1	42.9% (73)	16.1% (262)	21.6% (335)	
2	20% (34)	3.3% (54)	6.7% (88)	
3	10.6% (18)	0.9% (15)	2.9% (33)	
4	1.2% (2)	0.4% (7)	0.6% (9)	
Hypertension (%, n)	68.9% (126)	50.7% (822)	52.5% (948)	<0.0001
Diabetes (%, n)	33.9% (62)	25.5% (413)	26.3% (475)	0.04
Smoker (%, n)	2.9% (5)	12.2% (198)	11.3% (203)	<0.0001
BMI (mean, range)	31.6 (19–48)	32.3 (16.3–64.5)	32.2 (16.3-64.5)	0.2
Synchronous or metachronous tumors (%, n)	13.5% (23)	9.8% (159)	10.1% (182)	0.08

in BMI, although younger women showed a tendency to higher BMI (32.3 vs. 31.6). More than 50% of the total population suffered from hypertension and more than 25% were diabetic; however, elderly patients had significantly more comorbidities. Furthermore, patient's aged 80 or older presented significantly more ECOG status ≥2 than the younger ones. Table 1 shows the clinical characteristics of these patients.

More than 90% of all patients had undergone surgery; however, only 68.2% of elderly patients had been surgically treated. The proportion of patients receiving palliative treatment was significantly higher among the elderly as compared to younger ones (27.6% vs. 4%). Dividing by age groups, patients younger than 40 years received palliative treatment only in 3.1%, between 40–49 years 1.9%, 50–59 2.3%, 60–69 3.5%, 70–79 7.1% and it increases dramatically from the age of 80 to 27.6% ($p < 0.0001$). Similarly, staging surgery was performed in only 10.3% of elderly patients, whereas it was carried out in more than 26% of younger ones. It is worth noting that no significant differences were found in the surgical approach between the elderly and the younger patients. In regard to intraoperative complications, no significant differences were found between both groups, while there was a higher rate of grade III and IV postoperative complications in patients aged 80 or older (12.9% vs 7.8%, $p = 0.04$). Table 2 shows the surgical and anatomo-pathological characteristics of the studied population.

Endometrioid tumors were more frequently diagnosed in younger patients (78.8% vs. 62.9%), while more aggressive cancer types, such as serous tumor, clear cell tumor or carcinosarcoma appeared more often in elderly patients. Similarly, the proportion of high-risk tumors was significantly higher in elderly patients while the proportion of low-risk tumors was significantly higher in younger patients.

Table 2
Surgical and anatomo-pathological characteristics of the studied population (EC = endometrial cancer, RT = radiotherapy, CT = chemotherapy, HT = hysterectomy, BSO = bilateral salpingo-oophorectomy, LPC = laparoscopy, LPT = laparotomy, MMMT = mullerian mixed malignant tumor, G = grade, FIGO = international federation of gynecology and obstetrics, ESGO = European Society of Gynecology Oncology). [*Grade III and IV complications of the Clavien-Dindo classification system, **Low-risk = grade 1 or 2 and superficial myometrial invasion<50%, Intermediate-risk = deep myometrial invasion>50% or grade 3 superficial myometrial invasion<50%, High-risk = grade 3 with deep myometrial invasion>50%].

	≥80 years (n = 170)	<80 years (n = 1629)	All patients (n = 1799)	p
Surgery (%, n)	68.2% (116)	92.4% (1505)	90.1% (1621)	<0.0001
Treatment modality	42.9% (73)	45.1% (734)	44.9% (807)	<0.0001
Surgery exclusive	25.3% (43)	47.3% (771)	45.2% (814)	
Surgery +/-RT+/-CT	4.1% (7)	3.6% (59)	3.7% (66)	
CT+/-RT	27.6% (47)	4% (65)	6.2% (112)	
Palliative				
Type of surgery (%, n)	89.7% (104)	73.8% (1111)	75% (1215)	<0.0001
HT+/-BSO	10.3% (12)	26.2% (394)	25% (406)	
HT+/-BSO + staging				
Surgical approach (%, n)	49.1% (57)	57.3% (863)	56.8% (920)	0.1
Laparotomy	46.6% (54)	36.8% (554)	37.5% (608)	
Laparoscopy	0.9% (1)	0.7% (10)	0.7% (11)	
Conversion LPC-LPT	3.4% (4)	5.2% (78)	5.1% (82)	
Vaginal				
Surgical complications (%, n)	2.6% (3)	3% (45)	3% (48)	0.5
Intraoperative complications	12.9% (15)	7.8% (117)	8.1% (132)	0.04
Postoperative complications*				
Histological type (%, n)	62.9% (107)	78.8% (1284)	77.3 (1391)	<0.0001
Endometrioid	18.2% (31)	7.7% (125)	8.7 (156)	
Serous	5.3% (9)	2.7% (44)	2.9 (53)	
Clear cell	6.5% (11)	4.5% (74)	4.7 (85)	
MMMT	7.1% (12)	6.3% (102)	6.3 (114)	
Other				
Histological type (%, n)	62.9% (107)	78.8% (1284)	77.3% (1391)	<0.0001
Type 1-EC	37.1% (63)	21.2% (345)	22.7% (408)	
Type 2-EC				
ESGO risk groups (%, n)**	45.3% (77)	69.7% (1136)	67.4% (1213)	<0.0001
Low-risk	15.9% (27)	23.4% (382)	24.4% (439)	
Intermediate-risk	33.5% (57)	6.2% (101)	7.1% (128)	
High-risk	5.3% (9)	1.1% (10)	1.1% (19)	
Unknown				
Tumor differentiation (%, n)	34.1% (58)	49.5% (807)	48.1% (865)	<0.0001
G1	15.9% (27)	21.5% (350)	21% (377)	
G2	44.7% (76)	28.4% (462)	29.9% (538)	
G3	5.3% (9)	0.6% (10)	1.1% (19)	
Unknown				
FIGO stage (%, n)	58.8% (100)	81.5% (1327)	79.3% (1427)	<0.0001
I-II	14.1% (24)	14.2% (231)	14.2% (255)	
III-IV	27.1% (46)	4.4% (70)	6.5% (117)	
Clinical staging				
Myometrial invasion (%, n)	42.4% (72)	67.6% (1102)	65.3% (1174)	<0.0001
None or <50%	24.1% (41)	23% (374)	23.1% (41)	
≥50%	33.5% (57)	9.4% (153)	11.7% (210)	
Unknown				
Adjuvant therapy to surgery (%, n)	37.1% (43/116)	51.2% (771/1505)	50.2% (814/1621)	0.002
Radiotherapy	100% (43)	84.3% (650)	85.1% (693)	0.001
CT +/-RT	–	15.7% (121)	14.9% (121)	–
Tumor progression/persistence (%, n)	39.4% (67)	11.4% (186)	14.1% (253)	<0.0001
Recurrence (%, n)	10% (17)	10.5% (171)	10.5% (188)	0.4
Death due to disease (%, n)	43.5% (74)	20.1% (328)	22.3% (402)	<0.0001

More than 50% of patients received adjuvant therapy postoperatively, which corresponded to 51.2% of younger patients and 37.1% of elderly ones. The most frequently used treatment was radiotherapy, although more than 15% of younger patients received chemotherapy. None of the elderly patients was subjected to cytostatic treatment. Tumor progression or persistence of malignancy was detected in 14.1% of all cases, corresponding to 11% of younger patients and 39.4% of elderly ones. No differences were found in recurrence rates between groups; 10.5% of all patients experienced recurrence with a median time interval of 17.5 months (range 6–135 months) between the initial treatment and the recurrence.

The mean cancer specific-survival for all patients was 217.7 months (95%CI 210.7–224.7), with a 5 year and 10 year cancer specific-survival of 74.9% and 71%, respectively. The cancer specific-survival in older patients was significantly lower than in younger ones: mean cancer specific-survival 61.4 months (95%CI 51.7–71.1) versus 226 months (95%CI 218.9–233.1) respectively ($p < 0.0001$) (Fig. 1A and B).

In a multivariate analysis, variables: age (OR 1.7; 95%CI, 1.1–2.5; $p = 0.01$), stage (II vs. I OR 2.1; 95%CI, 1.4–3.2; III vs. I OR 5.5; 95%CI, 4.1–7.5 and IV vs. I OR 4.8; 95%CI, 2.9–7.8; $p < 0.0001$), histology (type-2 vs. type-1 OR 1.5; 95%CI, 1.1–2.2; $p < 0.0001$), tumor differentiation (2 vs. 1 OR 2.5; 95%CI, 1.6–4.1 and 3 vs. 1 OR 5.8; 95% CI, 3.5–9.7 $p < 0.0001$) and adjuvant treatment (yes vs. no OR 0.6; 95%CI, 0.4–0.9; $p = 0.01$) were all independently associated with cancer specific-survival (Table 3).

Discussion

The number of EC cases has significantly increased in European countries in the last decades. Furthermore, given the progressive aging of Western populations, the amount of elderly women with EC is expected to increase in the coming years. In our series, the percentage of EC patients of 80 years of age or older increased more than four times in the last 25 years, from 3.1% to more than 14%. Thus, today the management of these patients can be considered a frequent clinical practice, which raises concern among the involved healthcare professionals.

Several multicentric studies evidenced that elderly EC patients are more likely to present with non-endometrioid, undifferentiated tumors at an advance stage. Whereas, they are less likely to receive lymphadenectomy, radiotherapy and systemic treatments, and show poorer cancer specific-survival than younger patients [3,6,7,9–12]. Accordingly, elderly patients in our series were diagnosed with histologically more aggressive disease at more advanced stages, received less surgery, staging and adjuvant treatments, had a higher probability of receiving palliative treatment and showed poorer cancer specific-survival. Several studies have demonstrated that chemotherapy in elderly patients is feasible, with an acceptable toxicity profile [12,13]. Similarly, radiotherapy seems to be safe in older patients, e.g. no differences were found between younger and older EC patients in late radiation toxicity [14,15]. Despite these evidences, elderly patients continue to receive less adjuvant radio- or chemotherapy, even when guidelines indicate adjuvant treatment according to the tumor status. Table 4 reviews the updated medical data of patients with EC aged 80 and older.

A minimally invasive approach, i.e. laparoscopy, is preferred in the surgical treatment of EC, because it is associated with shorter hospital stay, shorter recovery time, less postoperative discomfort and generally better quality of life, as compared to laparotomy [16,17]. Several studies have demonstrated the feasibility and safety of laparoscopic surgery in older patients; a minimally invasive approach to uterine cancer staging may decrease their morbidity and influence their long-term survival [18,19]. In our series, the proportion of laparoscopic interventions was similar in younger and elderly patients, which indicates that age *per se* is not a contraindication for minimally invasive surgery. Moreover, several studies demonstrate the viability, safety and good short-term results of robotic surgery in elderly patients with gynecological cancer (20,21)

The role of lymphadenectomy in EC staging is a highly debated topic, especially in elderly patients. This procedure prolongs operative times and increases complication rates. In elderly patients, there is also an increased risk of intraoperative vascular complications due to the high frequency of atherosclerosis [22]. The use of lymphadenectomy in elderly women with EC is controversial among surgeons and many authors generally omit retroperitoneal staging in these patients [8,10]. In our series, like in other studies, elderly patients underwent less lymphadenectomy than younger ones [6]. These findings indicate the need for an in-depth evaluation of the possible impact of lymphadenectomy on survival, in order to assess the benefits of this procedure versus its possible complications, especially in this group of patients.

Studies comparing outcomes of very elderly women with EC versus younger women, find a similar rate of perioperative

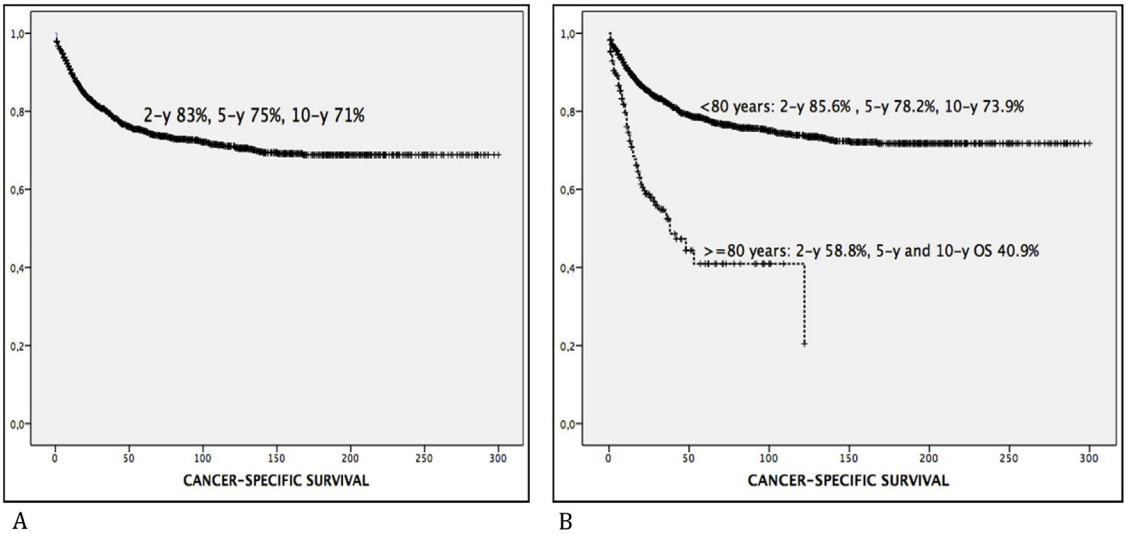

Fig. 1. A and B. Cancer-specific survival for all patients (n = 1799) and according to age ($p < 0.0001$).

Table 3
Multivariate analysis to assess the independent effect of each variable on cancer-specific survival (FIGO = International Federation of Gynecology and Obstetrics).

	OR	95%CI (inferior)	95%CI (superior)	p
Age <80 vs. ≥ 80	1.7	1.1	2.5	0.01
FIGO stage	2.1	1.4	3.2	<0.0001
II vs. I	5.5	4.1	7.5	
III vs. I	4.8	2.9	7.8	
IV vs. I				
Histological type 2 vs. 1	1.5	1.1	2.2	0.01
Tumor differentiation	2.5	1.6	4.1	<0.0001
2 vs. 1	5.8	3.5	9.7	
3 vs. 1				
Adjuvant treatment Yes vs. No	0.6	0.4	0.9	0.01

Table 4
Recent studies reporting patients aged 80 or older with endometrial cancer (NR = not reported, FIGO = International Federation of Gynecology and Obstetrics, ECOG = Eastern Cooperative Oncology Group; ASA = American Society of Anesthesiologists;=, OS = overall survival, DFS = disease free survival, CSS = cancer-specific survival, * Accordion Severity classification system, * *Clavien-Dindo classification system).

Author, year	N (age range)	Comorbidities	Surgical approach	Complications	FIGO stage	Histological type	Histological grade	Radiation therapy	Systemic treatment	Survival
Lowe et al, 2010 [9]	27 (80-95)	Hypertension 74% Diabetes mellitus 22%	100% robotic surgery	Intraoperative 7.4% Postoperative 33%	I 64% II 24% III-IV NR	NR	NR	NR	NR	NR
Bogani et al, 2014 [10]	63 (80-93)	ECOG-PS≥ 2 22% ASA score ≥3 23.8%	Laparoscopy 35% Laparotomy 40% Vaginal 25%	Intraoperative 0% Postoperative (all grade*) 19% Postoperative (grade ≥2) 11%	I 76% II-IV 24%	Endometrioid 73% Non-endometrioid 27%	1-2 71.4% 3 28.6%	22.2%	1.5%	5-y OS 80%
Zeng et al, 2015 [11]	31 (81-93)	ASA ≥3 47%	100% robotic surgery	Grade III-IV** 10%	I 65% II 6% III 29%	Endometrioid 75% Non-endometrioid 25%	NR	NR	NR	2-y DFS 80%
Clark et al, 2016 [12]	65 (80-89)	NR	NR	NR	I 66% II 9% III 18% IV 8%	Endometrioid 58% Non-endometrioid 42%	1 22% 2 17% 3 62%	NR	NR	NR
Eggemann et al, 2017 [6]	161 (81-93)	ECOG 0 25.7% ECOG 1 32.2% ECOG 2 31.6% ECOG 3 10.5%	Laparotomy 83.6% Vaginal 9.3% No 7.1%	NR	I 67.9% II 13.6% III 13.6% IV 5%	Endometrioid 89% Non-endometrioid 11%	1 21.3% 2 43.3% 3 35.3%	46%	0%	10-y OS 41.6%
Torgeson et al, 2017 [3]	5439 (NR)	Charlson 0 72% Charlson 1 22% Charlson 2 + 6%	NR	NR	I 59% II 18% III 22% IV 1%	NR	1 22% 2 40% 3 35% Undifferentiated 3%	34%	11%	NR
Poupon et al, 2017 [7]	120 (81-88)	Hypertension 54% Diabetes mellitus 20%	Laparoscopy 46% Laparotomy 37% Vaginal 10% NR 7%	NR	I 68% II 12% III 18% IV 2%	Endometrioid 75% Non-endometrioid 20% NR 5%	1 38% 2 29% 3 30% NR 3%	28%	4%	5-y DFS 70% 5-y CSS 78%
Current study, 2019	170 (80-93)	ECOG 0 25.3% ECOG 1 42.9% ECOG 2 20% ECOG 3 10.6% ECOG 4 1.2%	Laparoscopy 46.6% Laparotomy 49.1% Vaginal 3.4% Conversion 0.9%	Intraoperative 2.6% Postoperative (grade ≥3) 12.9%	I-II 58.8% III-IV 14.1% Other 27.1%	Endometrioid 62.9% Non-endometrioid 37.1%	1 34.1% 2 15.9% 3 44.7% NR 5.3%	37.1%	0%	5-y and 10-y CSS 40.9%

complications between both groups, while surgical management of EC in this age group is frequently associated to a higher rate of major postoperative complications, possibly due to the high comorbidities rate, as in our data [9–11]. In this regard, a point worth mentioning is the place of the enhanced recovery pathway in gynecologic oncology, an approach developed in recent years. The systematic implementation of an evidence-based perioperative care protocol has resulted in a decrease in complications by as much as 50% for patients undergoing colorectal surgery [23]. Similarly, available studies in gynecologic oncology demonstrate important improvements in postoperative recovery, patient satisfaction, and substantial cost reductions without additional

risk to the patient, regardless of age [23,24]. Different guidelines have been published in this regard, the last of which was published recently as an updated consensus review for the Enhanced Recovery After Surgery (ERAS) in gynecologic oncology [24]. The implementation of this multidisciplinary approach enhances surgical recovery through attenuation of the stress response with the goal of optimizing patient recovery, thus probably decreasing the rate of severe postoperative complications in patients aged 80 and older, and increasing the confidence of the treating physician in applying surgical treatments to this group of patients.

A number of studies have demonstrated worse prognosis in elderly EC patients, a finding also confirmed by our data [6,8]. It remains unclear whether such worse prognosis is attributable to age and its associated immunological decline, to inherently more aggressive disease, to the fact that aged patients receive less treatment, or to a combination of all these factors. The most common reason for not administering indicated treatments seems to be the physician's opinion that elderly patients may not tolerate the therapy, based on their performance status and comorbidities, rather than patient refusal. Such an opinion often prevails despite the fact that a number of prospective studies have demonstrated that elderly patients have similar preferences for radical surgery and curative treatment than younger ones [6,25].

Available scientific evidence suggests that age alone should not be a decision factor in the prescription of EC treatment in elderly women. In order to enhance the care of these patients and ensure proper surgical management, a multidisciplinary approach to treatment is necessary and age-related physiological changes should be considered together with accompanying comorbidities. Traditionally, in studies addressing therapeutic interventions in the elderly, patient management has been based on a stratification of their functionality through the ECOG scale or the Karnofsky Index. However, studies have demonstrated that 80% of older-than-70 cancer patients show ECOG scale status 0 or 1; in our study 68.2% of patients aged 80 and older were ECOG 0–1 [26]. These scales leave aside transcendental aspects in the geriatric assessment, such as performance in basic and instrumental activities of daily life, cognitive performance, nutritional status and concomitant diseases; all of which are well correlated with functional status and vulnerability, and are associated with adverse outcomes in geriatric patients undergoing medical treatment for cancer. A systematic and evidence-based approach is needed to guide oncologic treatment decisions, hence the concept of Comprehensive Geriatric Assessment (CGA) [27]. The CGA is defined as a multidimensional and interdisciplinary diagnostic process focused on determining the medical, psychosocial and functional capacities of an older person, aimed at developing a coordinated and integrated long-term treatment and follow-up plan [28].

CGA importantly contributes to estimate life expectancy in the elderly and facilitates decision-making by helping differentiate between frail and non-frail elders. Most authors agree that frailty corresponds to a reduction in physiological reserves that limits the patient's ability to respond to stress and predisposes to adverse events [29,30]. Several publications have shown that CGA may lead to substantial modification of the therapeutic approach initially proposed by the specialist [31,32]. Furthermore, recent reports in medical oncology and other specialties have strongly suggested that CGA can be useful in oncology to predict survival [33–36]. Specifically, in the discipline of gynecologic oncology, the preoperative assessment of frailty has been demonstrated to be well accepted by patients and to be feasible in the clinical setting; however, in our knowledge, its integration in treatment decision-making has never been prospectively evaluated [37–39].

EC represents the most common gynaecological malignancy in developed countries, mostly diagnosed and treated in early stages with a good prognosis [1,2]. Therefore an increasing number of patients with EC become long-term survivors representing quality-of-life a relevant aspect of the treatment. Traditionally, treatment for EC has focused almost exclusively on the prolongation of life, and relatively little research has been carried out on quality-of-life in these patients. Furthermore, the treatment of early-stage EC has changed considerably over the years, with increasing use of minimally invasive surgery, lymphadenectomy only performed in selected cases, omission of adjuvant radiotherapy in low-risk patients, etc [40]. Therefore, the quality of care of all these therapeutic interventions needs to be evaluated not only by the clinicians but also by the patients. The increasing availability of data on the quality of inpatient care based on patient reported outcome measures (PROMs) and patient reported experience measures (PREMs) provide insight into the experience of EC survivors from the patient perspective. In recent studies evaluating overall quality-of-life in EC survivors, no significant differences were found from that of healthy women only 3 years post-diagnosis, so patients treated for early-stage EC, regardless of age, should be informed about the low risk of psychosocial and physical long-term effects [41, 42]. These findings may also encourage elderly patients with EC to undergo the standard treatments for this condition.

The present study has certain limitations, such as its retrospective design, and the fact that no standardized criterion was used over the years to identify elderly patients who could benefit from a curative treatment, but the subjective opinion of the physician in charge, based on patient's age and comorbidities. The strengths of the study include that, as far as we know, this is the largest elderly patient population, who were managed in a single centre, with a prolonged follow-up period with a minimum amount of losses.

In summary, the incidence of EC increases with population aging and is highest in advanced age groups. This study provides evidence that EC patients often suffer from more aggressive disease, receive less treatment with curative intent and consequently show poorer survival. Age *per se* is not a good predictor of treatment-associated morbidity; we postulate that planning a patient's treatment exclusively on the basis of their age should not be acceptable. Therefore, validated scales for oncogeriatric evaluation are needed with the aim of optimizing the therapeutic approach and treatment of elderly EC patients, thus improving prognosis in this population.

Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

[1] Data source: Globocan 2018. Graph production: global Cancer observatory. International Agency for Research on Cancer; 2018. http://gco.iarc.fr.
[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359–386.
[3] Torgeson A, Boothe D, Poppe MM, Suneja G, Gaffney DK. Disparities in care for elderly women with endometrial cancer adversely effects survival. Gynecology Oncology 2017;147(November 2):320–8.
[4] Abellán A, Ayala A, Pérez J, Pujol R, Un perfil de las personas mayores en España. Indicadores estadísticos básicos. Madrid, Informes Envejecimiento en red nº 17 34p. Cited: 07/02/2018. 2018.
[5] Population ageing in Europe. Facts, implications and policies. Directorate-general for research and innovation socioeconomic sciences and humanities. European Union 2014 Cited: 31/01/2019.
[6] Eggemann H, Ignatov T, Burger E, Dan Costa S, Ignatov A. Management of elderly women with endometrial cancer. Gynecol Oncol 2017;146(September 3):519–24.
[7] Poupon C, Bendifallah S, Ouldamer L, Canlorbe G, Raimond E, Hudry N, et al. Management and survival of elderly and very elderly patients with endometrial Cancer: an age-stratified study of 1228 women from the FRANCOGYN group. Ann Surg Oncol 2017;24(June 6):1667–76.

[8] Bourgin C, Saidani M, Poupon C, Cauchois A, Foucher F, Leveque J, et al. Endometrial cancer in elderly women: which disease, which surgical management? A systematic review of the literature. Eur J Surg Oncol 2016;42(Feburary 2):166–75.
[9] Lowe MP, Kumar S, Johnson PR, Kamelle SA, Chamberlain DH, Tillmanns TD. Robotic surgical management of endometrial cancer in octogenarians and nonagenarians: analysis of perioperative outcomes and review of the literature. J Robot Surg 2010;4(August 2):109–15.
[10] Bogani G, Cromi A, Uccella S, Serati M, Casarin J, Pinelli C, et al. Perioperative and long-term outcomes of laparoscopic, open abdominal, and vaginal surgery for endometrial cancer in patients aged 80 years or older. Int J Gynecol Cancer 2014;24:894–900.
[11] Zeng XZ, Lavoue V, Lau S, Press JZ, Abitbol J, Gotlieb R, et al. Outcome of robotic surgery for endometrial cancer as a function of patient age. Int J Gynecol Cancer 2015;25(May 4):637–44.
[12] Clark LH, Jackson AL, Gehrig PA, Bae-Jump V, Van Le L, Ko EM. Adjuvant treatment and clinical trials in elderly patients with endometrial Cancer: a time for change? Int J Gynecol Cancer 2016;26(February 2):282–9.
[13] Palaia I, Loprete E, Musella A, Marchetti C, Di Donato V, Bellati F, et al. Chemotherapy in elderly patients with gynecological cancer. Oncology 2013;85(3):168–72.
[14] Fiorentino A, Chiumento C, Fusco V. Do comorbidity influences acute toxicity and outcome in elderly patients with endometrial cancer treated by adjuvant radiotherapy plus brachytherapy? Clin Transl Oncol 2013;15(August 8):665–9.
[15] Zachariah B, Balducci L, Venkattaramanabalaji GV, Casey L, Greenberg HM, DelRegato JA. Radiotherapy for cancer patients aged 80 and older: a study of effectiveness and side effects. Int J Radiat Oncol Biol Phys 1997;39(December 5):1125–9.
[16] Lu Q, Liu H, Liu C, Wang S, Li S, Guo S, et al. Comparison of laparoscopy and laparotomy for management of endometrial carcinoma: a prospective randomized study with 11-year experience. J Cancer Res Clin Oncol 2013;139:1853–9.
[17] Galaal K, Donkers H, Bryant A, Lope AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev 2018;31(October 10).
[18] Ciavattini A, Di Giuseppe J, Cecchi S, et al. Gynecologic laparoscopy in patients aged 65 or more: feasibility and safety in the presence of increased comorbidity. Eur J Obstet Gynecol Reprod Biol 2014;175:49–53.
[19] Bishop EA, Java JJ, Moore KN, Spirtos NM, Pearl ML, Zivanovic O, et al. Surgical outcomes among elderly women with endometrial cancer treated by laparoscopic hysterectomy: a NRG/Gynecologic Oncology Group study. Am J Obstet Gynecol 2018;218(January 1):109.e1–109.e11.
[20] Gallotta V, Conte C, D'Indinosante M, Federico A, Biscione A, Vizzielli G, et al. Robotic surgery in elderly and very elderly gynecologic Cancer patients. J Minim Invasive Gynecol 2018;25(5):872–7.
[21] Lavoue V, Gotlieb W. Benefits of minimal access surgery in elderly patients with pelvic Cancer. Cancers (Basel). 2016;8(1).
[22] Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg 2006;203:865–77.
[23] Nelson G, Kalogera E, Dowdy SC. Enhanced recovery pathways in gynecologic oncology. Gynecol Oncol 2014;135(December 3)586–94 Review.
[24] Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A. Meyer LA at al. Guidelines for perioperative care in gynecologic/oncology: enhanced Recovery after Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer 2019(Mar 15).
[25] Nordin AJ, Chinn DJ, Moloney I, Naik R, de Barros Lopes A, Monaghan JM. Do elderly cancer patients care about cure? Attitudes to radical gynecologic oncology surgery in the elderly. Gynecol Oncol 2001;81(June 3):447–55.
[26] Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with Cancer. J Clin Oncol 2007;25:1824–31.
[27] Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. Cancer 2005;104(1998).
[28] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patientswith cancer. J Clin Oncol 2014;32(August 24):2595–603.
[29] Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.
[30] Molina MJ, Oncogeriatría Guillén C. Una forma de optimizar la atención global del paciente anciano con cáncer. Nutr Hosp 2016;33(Supl. 1):31–9.
[31] Chaïbi P, Magné N, Breton S, Chebib A, W atson S, Duron JJ, et al. Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. Crit Rev Oncol Hematol 2011;79:302–7.
[32] Girre V, Falcou MC, Gisselbrecht M, Gridel G, Mosseri V, Bouleuc C, et al. Does a geriatric oncology consultation modify the cancer treatment plan for elderly patients? J Gerontol A Biol Sci Med Sci 2008;63(July 7):724–30.
[33] Shahrokni A, Vishnevsky BM, Jang B, Sarraf S, Alexander K, Kim SJ, et al. Geriatric assessment, not ASA physical status, is associated with 6-Month postoperative survival in patients with Cancer Aged ≥75 years. J Natl Compr Canc Netw 2019;17(June 6):687–94.
[34] Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for vulnerability in older cancer patients: the ONCODAGE prospective multicenter cohort study. PLoS One. 2014;9(December 12).
[35] Maione P, Perrone F, Gallo C, Manzione L, Piantedosi F, Barbera S, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23(October 28):6865–72.
[36] Pardal E, Díez Baeza E, Salas Q, García T, Sancho JM, Monzón E, et al. GELTAMO Spanish Collaborative Group. A new prognostic model identifies patients aged 80 years and older with diffuse large B-cell lymphoma who may benefit from curative treatment: a multicenter, retrospective analysis by the Spanish GELTAMO group. Am J Hematol 2018;93(July 7):867–73.
[37] Courtney-Brooks M, Tellawi AR, Scalici J, Duska LR, Jazaeri AA, Modesitt SC, et al. Frailty: an outcome predictor for elderly gynecologic oncology patients. Gynecol Oncol 2012;126(July 1):20–4.
[38] Kumar A, Langstraat CL, DeJong SR, McGree ME, Bakkum-Gamez JN, Weaver AL, et al. Functional not chronologic age: frailty index predicts outcomes in advanced ovarian cancer. Gynecol Oncol 2017;147(October 1):104–9.
[39] Duska L, Shahrokni A, Powell M. Treatment of older women with endometrial Cancer: improving outcomes with personalized care. Am Soc Clin Oncol Educ Book 2016;35:164–74.
[40] Ferguson SE, Panzarella T, Lau S, Gien LT, Samouëlian V, Giede C, et al. Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer. Gynecol Oncol 2018;149(June (3)):476–83.
[41] Shisler R, Sinnott JA, Wang V, Hebert C, Salani R, Felix AS. Life after endometrial cancer: a systematic review of patient-reported outcomes. Gynecol Oncol 2018;148(February 2):403–13.
[42] Dobrzycka B, Terlikowski R, Kulesza-Brończyk B, Niklinski J, Terlikowsk SJ. Quality of life in long-term survivors of early stage endometrial cancer. Ann Agric Environ Med 2017;24(September 3):513–6.