Drugs - Real World Outcomes (2018) 5:225–235
https://doi.org/10.1007/s40801-018-0145-x

ORIGINAL RESEARCH ARTICLE

Impact of Age, Comorbidity, and FIGO Stage on Treatment Choice and Mortality in Older Danish Patients with Gynecological Cancer: A Retrospective Register-Based Cohort Study

Sambavy Nadaraja[1,2] · Trine Lembrecht Jørgensen[1] · Lars-Erik Matzen[3] · Jørn Herrstedt[1,4]

Published online: 20 November 2018

Abstract

Background The number of older patients with cancer is increasing in general, and ovarian and endometrial cancer are to a large extent cancers of the elderly. Older patients with cancer have a high prevalence of comorbidity. Comorbidity and age may be predictive of treatment choice and mortality in older patients with cancer along with stage and performance status.

Objectives The aim of this study was to describe comorbidity in a population of older Danish patients with gynecological cancer, and to evaluate the predictive value of comorbidity and age on treatment choice and cancer-specific and all-cause mortality.

Materials and methods In this retrospective study, we included 459 patients aged ≥ 70 years. Patients were diagnosed with cervical, endometrial, or ovarian cancer from 1 January, 2007 to 31 December, 2011 and were evaluated and/or treated at Odense University Hospital. Comorbidity was assessed using the Charlson Comorbidity Index. Treatment was classified as curative intended, palliative intended, or no treatment.

Results Age, International Federation of Gynecology and Obstetrics (FIGO) stage, and performance status were found to be significant predictors of treatment choice, while comorbidity was not. Multivariate analyses showed that both cancer-specific and all-cause mortality were significantly associated with treatment choice, FIGO stage, and performance status. Age was not associated with mortality, with the exception of ovarian cancer, where age was associated with all-cause mortality. Comorbidity was not an independent predictor of treatment choice or mortality.

Conclusions In our population of older Danish patients with gynecological cancer, age, FIGO stage, and performance status were predictors of treatment choice, while comorbidity was not. Treatment choice, FIGO stage, and performance status were significantly associated with both cancer-specific and all-cause mortality. Age was only associated with mortality in ovarian cancer, while comorbidity was not associated with mortality.

Key Points

Significant predictors of treatment choice in older patients with gynecological cancer include age, International Federation of Gynecology and Obstetrics (FIGO) stage, and performance status, but not comorbidity

Significant predictors of both cancer-specific and all-cause mortality in older patients with gynecological cancer were treatment choice, FIGO stage, and performance status

Age was only a significant predictor of mortality in patients with ovarian cancer

✉ Sambavy Nadaraja
sambavy.nadaraja@rsyd.dk

1 Department of Oncology, Odense University Hospital, Onkologisk afdeling R, Sdr. Boulevard 29, Indgang 109, 5000 Odense C, Denmark

2 Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

3 Department of Geriatric Medicine, Odense University Hospital, Odense, Denmark

4 Department of Clinical Oncology, Zealand University Hospital, Roskilde, Denmark

1 Introduction

The number of older patients with cancer is increasing as a result of the aging population. Today, almost half of all cancer survivors (47%) in USA are aged 70 years or older [1]. Gynecological cancers include malignancies of the uterine cervix, endometrium, ovaries, fallopian tubes, peritoneum, vagina, and vulva. A recent study, examining trends in gynecological cancers in older women, found that women aged 70 years and above with cervical, endometrial, or ovarian cancer had a two to three times higher mortality rate compared with women aged < 70 years. This was the case despite different characteristics regarding etiology, incidence, stage at diagnosis, and treatment options [2].

Comorbidity is defined as the presence of additional diseases in relation to an index disease in one individual [3]. Older patients with cancer have a higher number of comorbidities than younger patients, and the likelihood of co-existing conditions increases with age. Depending on the number and severity of comorbid conditions, these might have an impact on patients' health status and their treatment. In addition to comorbidity itself, age has been shown to be a significant predictor of comorbid death [4]. Comorbidity has an impact on the toxicity of a given treatment in older patients with cancer [5] and therefore might influence the treatment offered. An earlier study found that age ≥ 70 years as well as severe comorbidity, expressed by a score of ≥ 3 in the American Society of Anesthesiologists (ASA) physical status classification system, were independent predictors for not undergoing surgery or receiving standard combination chemotherapy in patients with ovarian cancer [6]. The aim of this study was to describe comorbidity in a population of older patients with gynecological cancer, and to evaluate the predictive value of comorbidity and age on treatment choice and cancer-specific and all-cause mortality.

2 Materials and Methods

This is a retrospective register-based cohort study. The study population consists of women aged 70 years or more, diagnosed with gynecological cancer from 1 January, 2007 to 31 December, 2011 at the Department of Gynecology and Obstetrics at Odense University Hospital located in Southern Denmark. The patients were evaluated and/or treated for their malignant disease in this department and/or in the Department of Oncology at the same center. The center treats residents of Funen, which comprises 9% of the Danish population in addition to the majority of Southern Jutland, and a previous validation study has concluded that the population of Funen is representative of the entire Danish population [7]. The diagnoses included were cervical cancer [International Classification of Diseases, 10th Revision (ICD-10)] (code C53), endometrial cancer (codes C54–55), ovarian cancer (code C56), fallopian tube cancer (code C57), and primary peritoneal cancer (code C48). Cancers of the ovaries, fallopian tubes, and peritoneum were considered as one entity and will be referred to as "ovarian cancer" in this article. Only patients with epithelial ovarian cancers were included and patients with borderline tumors were excluded.

2.1 Data Sources

All Danish citizens have been assigned a personal identification number since 1968. This enables linkage of data from different registers and databases [8]. Eligible patients were identified in The Danish Gynecological Cancer Database (DGCD). All pathology results of the patients were reviewed to confirm diagnoses. Supplementary data were obtained from the Danish Causes of Death Register and the National Patient Register (NPR), in addition to the medical charts of the patients.

The DGCD is a nationwide multidisciplinary clinical database. It contains disease-specific information on women diagnosed with gynecological cancer from 1 January, 2005 and onward. There are three categories of data available; surgical, pathological, and oncological. Variables available in the DGCD include date of diagnosis, performance status (PS), date and extent of surgery, stage, histological type and grading, residual disease, and intended treatment. A validation study found that data on surgery and pathology were valid for research [9]. Data on oncological treatment were incomplete and have been omitted since July 2013.

Information regarding all deaths in Denmark is collected in the Danish Causes of Death Register [10]. The information originates from death certificates, the completion of which became mandatory in 1871. It includes date and cause of death ranging from the main to the contributory and immediate causes for each individual. Causes of death are coded according to the ICD-10.

Where relevant data were not obtainable from the above-mentioned databases and registers, the medical charts of patients were reviewed. In particular, oncological data were supplemented from medical charts. Staging of the cancers was based on the International Federation of Gynecology and Obstetrics (FIGO) staging pooled into three groups: (1) FIGO stage I: localized tumors and (2) FIGO stage II and III: tumors with regional metastases and FIGO stage IV: tumors with distant metastases. Information regarding stage was obtained from the DGCD with supplementation from medical charts. Age at diagnosis

was divided into four age groups: (1) 70–74 years; (2) 75–79 years; (3) 80–84 years; and (4) ≥ 85 years.

The Charlson Comorbidity Index (CCI) is a weighted comorbidity index including 19 chronic conditions. The CCI has been validated in a population of patients with cancer [4, 11]. In our study, we included non-malignant comorbidity, and the CCI score was grouped into three categories: (1) no comorbidity: CCI score 0; (2) mild-to-moderate comorbidity: CCI score 1–2; and (3) severe comorbidity: CCI score ≥ 3. This grouping has been used in previous studies [12]. The CCI score was constructed from diagnoses in the NPR treated at Danish hospitals. The NPR was established in 1977 [13]. All inpatient and outpatient contacts are registered with an ICD-10 diagnosis code. Adaption of the CCI for use with ICD administrative data has been validated in older patients with cancer [14].

Permission was obtained from the Danish Health Authority (Journal no. 3-3013-1078/1/). The end of follow-up was June 2017 for date of death. Causes of death were available up to 31 December, 2015.

2.2 Definition of Intended Treatment Groups

All patients were divided into three groups based on the intended treatment: curative, palliative, or none. Below is a summary of the antineoplastic therapies used in the period 2007–2011 at the department.

Ovarian cancer: Curative intended treatment included primary surgery followed by postoperative chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery (if possible) and then additional postoperative chemotherapy. Chemotherapy included carboplatin and paclitaxel or carboplatin as a single agent. Palliative treatment consisted of chemotherapy only. Endometrial cancer: Curative intended treatment included surgery in the majority of patients. According to risk factors, adjuvant or supplemental radiotherapy or medical oncological treatment, primarily carboplatin and paclitaxel, was administered. Palliative treatment consisted of systemic treatment or radiotherapy. Cervical cancer: Curative intended therapy included surgery (stage IA–IIA), followed by radiotherapy in the case of high-risk or residual disease, or primary chemo-radiotherapy. This consisted of external beam radiation with weekly concomitant cisplatin (chemo-radiation), and vaginal brachytherapy (in patients who did not undergo surgery). Stage IIB and higher received curative chemo-radiation or palliative treatment. Palliative treatment consisted of systemic treatment, and in rare cases, radiotherapy. No treatment was defined as the absence of any surgical or oncological treatment and included patients who refused treatment or were too frail to receive any disease-oriented therapy.

2.3 Statistical Analysis

The Fisher's exact test was used to investigate a possible association between comorbidity and treatment choice, and between FIGO stage and treatment choice. The non-parametric K sample test for equality of medians was used to investigate if there was an association between age and treatment choice. Ordered logistic regression was used to examine if comorbidity, FIGO stage, and age were associated with treatment choice. We estimated variance inflation factors to investigate possible collinearity between explanatory variables. A variance inflation factor > 10.0 indicated collinearity. The Kaplan–Meier method was used to estimate all-cause mortality, calculating the time from the date of diagnosis until death, regardless of the cause of death, or end of the follow-up. The Log rank test was used to investigate whether there was a difference in survival according to the treatment planned. A multivariate competing risk analysis was performed to estimate sub-hazard ratios for the adjusted association between CCI groups and cancer-specific mortality, adjusting for FIGO stage, age, treatment choice, diagnosis, and PS. The covariates were selected based on clinical meaningfulness. The Cox proportional hazards regression model was used to assess the adjusted association between the CCI group (with a CCI score of 0 as the reference) and all-cause mortality from the date of diagnosis, adjusting for FIGO stage, age, treatment choice, diagnosis, and PS. The proportional hazards assumption was tested using Schoenfeld residuals, and the model was found fit for use. All statistical analyses were performed with STATA Version 15 (StataCorp LP, College Station, TX, USA). A result was considered statistically significant at p values < 0.05. The study was approved by the Danish Data Protection Agency (Journal no. 15/19896).

3 Results

A total of 459 patients were included, of whom 186 had ovarian cancer, 219 had endometrial cancer, and 54 had cervical cancer (Table 1). Two hundred and ninety-six patients (64.5%) received curative intended treatment, 121 patients (26.4%) received palliative treatment, while 42 patients (9.2%) did not receive any treatment at all.

3.1 Comorbidity

A total of 188 (41%) of the patients had at least one comorbidity. Overall, the three most common comorbidities were cerebrovascular disease (9.6%), chronic pulmonary disease (8.7%), and peripheral vascular disease (7.8%). These were also the three most common comorbidities in the palliative intended treatment and the no treatment groups. In the

Table 1 Patient characteristics

Cancer type	Ovarian	Endometrial	Cervical
Total, *n*	186	219	54
Age, median (IQR), years	76 (72–80)	76 (73–81)	78 (74–83)
FIGO stage, *n* (%)			
I	30 (16.1)	102 (46.6)	12 (22.2)
II–III	111 (59.7)	52 (23.7)	30 (55.6)
IV	43 (23.1)	10 (4.6)	10 (18.5)
Unknown	2 (1.1)	55 (25.1)	2 (3.7)
Intended treatment, *n* (%)			
Curative	79 (42.5)	188 (85.8)	29 (53.7)
Palliative	84 (45.2)	20 (9.1)	17 (31.5)
No treatment	23 (12.4)	11 (5.0)	8 (14.8)
Comorbidity, *n* (%)			
CCI 0	114 (61.3)	124 (56.6)	33 (61.1)
CCI 1–2	62 (33.3)	76 (34.7)	16 (29.6)
CCI 3+	10 (5.4)	19 (8.7)	5 (9.3)
Performance status, *n* (%)			
0	66 (35.5)	84 (38.4)	20 (37.0)
1	66 (35.5)	63 (28.8)	8 (14.8)
2	33 (17.8)	28 (12.8)	8 (14.8)
3	8 (4.3)	8 (3.7)	4 (7.4)
4	3 (1.6)	3 (1.4)	1 (1.9)
Unknown	10 (5.4)	33 (15.1)	13 (24.1)

CCI Charlson Comorbidity Index, *FIGO* International Federation of Gynecology and Obstetrics, *IQR* interquartile range

curative intended treatment group, the second most common comorbidity after cerebrovascular disease (9.5%) was non-complicated diabetes mellitus (8.8%). These patients also had a high prevalence of complicated diabetes mellitus. No significant association was found between comorbidity and treatment choice (Table 2).

3.2 Stage

The FIGO stage was available for 400 patients, and it was associated with choice of treatment (Table 3). Of the 59 patients with a missing stage, 55 had endometrial cancer. The difference in stages among treatment groups was statically significant ($p < 0.05$).

3.3 Age

In the curative intended treatment group, median age (range) was 76 (72–80) years, while it was 78 (74–81) years and 81 (76–86) years for the palliative and no treatment groups, respectively. The difference in age between treatment groups was statistically significant both overall ($p = 0.000$) and within each diagnosis (ovarian cancer: $p = 0.000$, endometrial cancer: $p = 0.002$, and cervical

Table 2 Distribution of diagnoses and Charlson Comorbidity Index (CCI) scores according to treatment choice groups

CCI score	Curative treatment *N* (%)	Palliative treatment *N* (%)	No treatment *N* (%)	*P* value
Ovarian cancer				
0	47 (59.5)	53 (63.1)	14 (61.0)	
1–2	26 (32.9)	28 (33.3)	8 (34.8)	
≥3	6 (7.6)	3 (3.6)	1 (4.3)	0.884
Endometrial cancer				
0	103 (54.8)	14 (70.0)	7 (63.6)	
1–2	69 (36.7)	4 (20.0)	3 (27.3)	
≥3	16 (8.5)	2 (10.0)	1 (9.1)	0.566
Cervical cancer				
0	16 (55.2)	12 (70.6)	5 (62.5)	
1–2	10 (34.5)	4 (23.5)	2 (25.0)	
≥3	3 (10.3)	1 (5.9)	1 (12.5)	0.865
All cancer sites				
0	166 (56.1)	79 (65.3)	26 (61.9)	
1–2	105 (35.5)	36 (29.8)	13 (31.0)	
≥3	25 (8.5)	6 (5.0)	3 (7.1)	0.474

Table 3 Distribution of diagnoses and International Federation of Gynecology and Obstetrics stages according to treatment choice groups

Stage	Curative treatment *N* (%)	Palliative treatment *N* (%)	No treatment *N* (%)	*P* value
Ovarian cancer				
I	28 (35.4)	0 (0.0)	2 (8.7)	
II–III	43 (54.4)	57 (67.9)	11 (47.8)	
IV	8 (10.1)	25 (29.8)	10 (43.5)	
Unknown	0 (0.0)	2 (2.4)	0 (0.0)	**0.000**
Endometrial cancer				
I	98 (52.1)	4 (20.0)	0 (0.0)	
II–III	47 (25.0)	5 (25.0)	0 (0.0)	
IV	3 (1.6)	4 (20.0)	3 (27.3)	
Unknown	40 (21.3)	7 (35.0)	8 (72.7)	**0.000**
Cervical cancer				
I	11 (37.9)	0 (0.0)	1 (12.5)	
II–III	16 (55.2)	10 (58.8)	4 (50.0)	
IV	2 (6.9)	6 (35.3)	2 (25.0)	
Unknown	0 (0.0)	1 (5.9)	1 (12.5)	**0.006**
All cancer sites				
I	137 (46.3)	4 (3.3)	3 (7.1)	
II–III	106 (35.8)	72 (59.5)	15 (35.7)	
IV	13 (4.4)	35 (28.9)	15 (35.7)	
Unknown	40 (13.5)	10 (8.3)	9 (21.4)	**0.000**

Bolded values represent statistically significant results

cancer: $p = 0.001$). When adjusting for comorbidity, stage, and PS, the association between age and treatment choice still persisted and was significant. This association was mainly seen in patients with ovarian cancer (Table 4). In summary, patients with higher age were less likely to receive more aggressive treatment.

3.4 Treatment Choice

Ordered logistic regression with curative treatment as a dependent variable and adjustment for comorbidity, FIGO stage, age, diagnosis, and PS showed that FIGO stage, age, and PS were significant predictors of treatment choice both when the diagnoses were pooled and when analyzed separately (Table 4). Thus, both higher FIGO stage and higher age resulted in less aggressive treatment. Comorbidity did not influence treatment choice after adjustment for the above-mentioned factors (Table 4).

3.5 Cancer-Specific and All-Cause Mortality

At the end of the follow-up, 171 patients were still alive, while 288 had died. Date of death could not be obtained for four patients, who were excluded from further analysis regarding survival. Cause of death was available for 278 patients. Cause of death was missing for six patients, who were excluded from the cancer-specific survival analysis.

Patients with ovarian cancer who received curative intended treatment had a median survival of 3.7 years [95% confidence interval (CI) 2.7–not reached], while those who received palliative treatment had a median survival of 1.3 years (95% CI 0.2–1.7). Those who received no treatment had a median survival time of 0.2 years (95% CI 0.1–0.4). None of the patients with endometrial cancer who received curative intended treatment had died at the time of the follow-up, while those who received palliative treatment had a median survival time of 0.5 years (95% CI 0.3–2.1). Those who received no treatment had a median survival time of 0.2 years (95% CI 0.1–0.6). Patients with cervical cancer

Table 4 Ordered logistic regression with curative treatment as the dependent variable and adjustment for all listed variables

	Overall, $n = 459$ Adjusted HR (95% CI)	Ovarian cancer, $n = 186$ Adjusted HR (95% CI)	Endometrial cancer, $n = 219$ Adjusted HR (95% CI)	Cervical cancer, $n = 54$ Adjusted HR (95% CI)
Comorbidity				
CCI 0	Ref.	Ref.	Ref.	Ref.
CCI 1–2	0.8 (0.4–1.4)	1.1 (0.5–2.3)	0.6 (0.1–2.9)	0.3 (0.0–2.4)
CCI 3+	0.5 (0.2–1.6)	0.5 (0.1–2.2)	0.7 (0.1–9.0)	1.2 (0.1–11.4)
FIGO stage				
I	Ref.	Ref.	Ref.	Ref.
II–III	**12.6 (4.6–34.2)**	**94.6 (13.9–641.8)**	1.6 (0.3–8.0)	4.4 (0.4–53.8)
IV	**44.9 (14.4-140.1)**	**210.2 (26.8–1647.6)**	**59.8 (6.2–577.8)**	**18.3 (1.2–288.7)**
Age, years				
70–74	Ref.	Ref.	Ref.	Ref.
75–79	**2.5 (1.3–4.9)**	**2.7 (1.2–5.8)**	4.6 (0.6–35.6)	0.9 (0.1–10.1)
80–84	**4.1 (1.8–9.3)**	**6.4 (2.1–19.5)**	3.1 (0.3–26.1)	7.5 (0.8–71.4)
≥ 85	**12.9 (4.8–35.2)**	**23.6 (4.7–118.9)**	**10.8 (1.1–110.5)**	6.5 (0.5–89.2)
Diagnosis				
Ovarian cancer	Ref.	Ref.	Ref.	Ref.
Endometrial cancer	0.1 (0.0–0.2)	–	–	–
Cervical cancer	0.6 (0.3–1.4)	–	–	–
Performance status				
0	Ref.	Ref.	Ref.	Ref.
1	1.3 (0.7–2.5)	1.5 (0.7–3.3)	1.7 (0.3–10.5)	1.7 (0.2–3.3)
2	**3.1 (1.4–6.6)**	**4.2 (1.5–11.4)**	3.5 (0.5–24.8)	5.3 (0.5–54.9)
3	**13.8 (3.6–53.7)**	**108.3 (9.6–1219.4)**	4.3 (0.3–73.0)	23.7 (0.9–642.6)
4	**25.0 (2.3–274.8)**	**41.2 (3.1–556.0)**	–	–

Bolded values represent statistically significant results

Note: Variance inflation factor for performance status = 1.20 and variance inflation factor for FIGO stage = 1.11

CCI Charlson Comorbidity Index, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics, *HR* hazard ratio, *Ref.* reference

who received curative treatment had a median survival time of 6.3 years (95% CI 3.2–not reached), while those who received palliative treatment had a median survival time of 1.5 years (95% CI 0.7–2.5). Those who received no treatment had a median survival time of 0.4 years (95% CI 0.01–3.4).

Multivariate analysis (pooling all three diagnoses) showed that both cancer-specific and all-cause mortality were significantly associated with treatment choice and FIGO stage (Tables 5 and 6). Age and comorbidity were not associated with mortality.

For patients with ovarian cancer, treatment choice and FIGO stage were significantly associated with both cancer specific and all-cause mortality. In addition, age was significantly associated with all-cause mortality, whereas comorbidity did not significantly influence mortality (Tables 5 and 6). For patients with endometrial cancer, no significant association was found between any of the adjustment factors (comorbidity, age, stage, treatment choice, and PS) and cancer-specific mortality. All-cause mortality was significantly associated with stage and treatment choice (Tables 5 and 6). For patients with cervical cancer, all-cause mortality was significantly associated with no treatment. The analysis regarding cancer-specific mortality could not be performed for patients with cervical cancer alone because of the low number of patients with this diagnosis (Tables 5 and 6).

Table 5 Cancer-specific mortality

	Overall, $n=459$ Adjusted SHR (95% CI)	Ovarian cancer, $n=186$ Adjusted SHR (95% CI)	Endometrial cancer, $n=219$ Adjusted SHR (95% CI)
Comorbidity			
CCI 0	Ref.	Ref.	Ref.
CCI 1–2	1.2 (0.8–1.6)	1.1 (0.7–1.6)	1.2 (0.5–2.9)
CCI 3+	1.1 (0.4–2.5)	0.7 (0.2–2.4)	1.8 (0.4–8.1)
FIGO stage			
I	Ref.	Ref.	Ref.
II–III	**2.7 (1.4–5.0)**	**3.1 (1.2–8.5)**	1.8 (0.7–4.8)
IV	**4.2 (2.0–8.6)**	**4.7 (1.7–13.3)**	4.6 (0.7–31.7)
Age, years			
70–74	Ref.	Ref.	Ref.
75–79	1.3 (0.9–2.0)	1.3 (0.8–1.9)	1.7 (0.6–4.9)
80–84	1.5 (0.9–2.6)	2.0 (1.0–3.9)	1.4 (0.5–4.0)
≥ 85	1.3 (0.6–2.9)	0.5 (0.1–2.1)	2.0 (0.5–7.8)
Treatment choice			
Curative treatment	Ref.	Ref.	Ref.
Palliative treatment	**2.1 (1.4–3.2)**	**2.1 (1.3–3.3)**	1.8 (0.5–6.2)
No treatment	**5.1 (2.4–10.9)**	**10.2 (4.2–24.8)**	1.3 (0.1–22.2)
Diagnosis			
Ovarian cancer	Ref.	–	–
Endometrial cancer	0.5 (0.3–0.8)	–	–
Cervical cancer	0.3 (0.1–0.6)	–	–
Performance status			
0	Ref.	Ref.	Ref.
1	1.1 (0.7–1.5)	1.0 (0.7–1.5)	0.5 (0.2–1.5)
2	1.0 (0.5–1.7)	0.7 (0.4–1.3)	1.5 (0.4–5.9)
3	0.5 (0.2–1.8)	0.2 (0.0–1.5)	2.3 (0.4–13.5)
4	**9.3 (2.8–31.0)**	**6.6 (2.5–17.3)**	–

Bolded values represent statistically significant results

Note: Competing risk analysis with adjustment for all listed variables. Analysis was not possible for cervical cancer because of a low number of patients

CCI Charlson Comorbidity Index, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics, *SHR* sub-hazard ratio, *Ref.* reference

Table 6 All-cause mortality

	Overall, $n=459$ Adjusted HR (95% CI)	Ovarian cancer, $n=186$ Adjusted HR (95% CI)	Endometrial cancer, $n=219$ Adjusted HR (95% CI)	Cervical cancer, $n=54$ Adjusted HR (95% CI)
Comorbidity				
CCI 0	Ref.	Ref.	Ref.	Ref.
CCI 1–2	1.0 (0.8–1.4)	0.9 (0.6–1.3)	1.2 (0.7–2.1)	2.1 (0.6–7.4)
CCI 3+	1.3 (0.7–2.2)	1.0 (0.4–2.2)	1.7 (0.6–5.2)	1.7 (0.4–7.5)
FIGO stage				
I	Ref.	Ref.	Ref.	Ref.
II–III	**2.5 (1.6–3.7)**	**2.5 (1.3–5.0)**	**3.0 (1.6–5.6)**	
IV	**3.9 (2.4–6.5)**	**4.1 (1.9–8.8)**	**6.2 (1.9–20.0)**	
Age, years				
70–74	Ref.	Ref.	Ref.	Ref.
75–79	1.2 (0.9–1.7)	1.2 (0.8–1.7)	1.7 (0.9–3.4)	1.6 (0.4–6.7)
80–84	1.3 (0.8–2.0)	**2.0 (1.1–3.4)**	0.6 (0.2–1.4)	0.8 (0.2–3.9)
≥85	1.6 (0.9–2.7)	2.8 (1.2–6.4)	1.1 (0.4–2.8)	0.6 (0.1–3.4)
Treatment choice				
Curative treatment	Ref.	Ref.	Ref.	Ref.
Palliative treatment	**2.7 (1.8–4.0)**	**2.1 (1.3–3.3)**	**12.9 (5.4–30.8)**	**3.0 (0.7–12.9)**
No treatment	**8.8 (4.9–15.8)**	**7.7 (3.2–18.1)**	**71.2 (7.9–643.8)**	**4.7 (2.1–56.7)**
Diagnosis				
Ovarian cancer	Ref.	–	–	–
Endometrial cancer	0.8 (0.6–1.3)	–	–	–
Cervical cancer	0.6 (0.3–0.9)	–	–	–
Performance status				
0	Ref.	Ref.	Ref.	Ref.
1	1.2 (0.9–1.7)	1.2 (0.8–1.8)	1.4 (0.7–2.7)	1.6 (0.4–6.2)
2	1.5 (1.0–2.2)	1.0 (0.6–1.8)	**3.2 (1.4–7.4)**	2.3 (0.5–10.4)
3	1.9 (0.9–3.7)	1.6 (0.5–4.9)	3.2 (0.8–13.2)	1.9 (0.2–16.7)
4	**9.4 (3.2–27.6)**	**8.0 (2.3–28.6)**	–	–

Bolded values represent statistically significant results

Note: Cox proportional hazards model with adjustment for all listed variables

CCI Charlson Comorbidity Index, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics, *HR* hazard ratio, *Ref.* reference

4 Discussion

Comorbid conditions are common in older patients with cancer, and these patients have a higher prevalence of comorbidity than age-matched controls without cancer [12]. In addition, it has been shown that the existence of comorbidity in patients with cancer influences prognosis, treatment choice, and overall survival [14].

The prevalence of comorbidity in our population was 41.0%, which is in line with earlier findings in an older population with various cancer diagnoses [15]. Age, FIGO stage, and PS were significant predictors of treatment choice, while comorbidity assessed as CCI was not. FIGO stage, PS, and treatment choice were significant predictors of both cancer-specific and all-cause mortality (for ovarian cancer, age was also a significant predictor of all-cause mortality), but comorbidity was not a significant predictor for mortality.

A previous Danish study including 1540 patients with ovarian cancer diagnosed between 2000 and 2011 found that 68% had a CCI score of 0, 23% had a score of 1–2, while the remaining 8% had a score of ≥3 [16]. This is comparable to our ovarian cancer population, although a CCI score of 1–2 was found in 33.3%. The same study found an increasing prevalence of comorbidity with increasing age during the study period, but with only little change in survival. They credit the centralization and more extensive surgery that has occurred in the same period as factors that have counteracted the decrease in survival that would have been expected [16].

The influence of comorbidity on survival in ovarian cancer is diverging, as some studies have reported that comorbidity impacts survival in this population [17–24],

while other studies, like ours, do not find this association [25–27]. Sperling et al. [17] found that PS mediates some of the impact of comorbidity on survival, as the hazard ratio decreased from 1.31 to 1.17, when including PS, and that comorbidity had a lesser impact on survival compared with other factors such as stage, PS, and residual tumor status. A meta-analysis exploring comorbidity and survival in patients with ovarian cancer, based on a limited number of studies including the one described above, found a hazard ratio of 1.20 (95% CI 1.11–1.30) for presence vs. absence of comorbidity [28]. The results of the study should be interpreted with caution, as it was not possible to control for potential confounders that were not included in the original studies. The studies were adjusted for different potential confounders, and the possibility of unmeasured or residual confounding could not be excluded [28].

Only a limited number of studies have been performed examining the association between comorbidity and treatment choice. Sperling et al. [17] did not find an association between comorbidity and surgical treatment choice. The authors interpreted their results of the lesser impact of comorbidity on survival as an indication that a treatment decision is primarily based on stage and PS. These results are in line with our finding that comorbidity did not impact treatment choice as much as age and FIGO stage. Noer et al. [29] also did not find an association between comorbidity and treatment choice, when adjusting for age and FIGO stage, in a population of 5317 patients with ovarian cancer. Another study has indicated that comorbidity may have a lesser impact on surgical treatment decisions than on chemotherapeutic treatment decisions for some cancers, but this has not been studied in gynecological cancer so far [30].

In a population of patients with stage I endometrial cancer aged ≥60 years, comorbidity did not influence surgery rate, but two or more comorbidities reduced the likelihood of receiving adjuvant radiotherapy (0.6, 95% CI 0.3–1.0) [31]. The same study found poorer survival in patients with comorbidity, especially those with comorbidities already associated with endometrial cancer that are related to obesity such as diabetes mellitus and cardiovascular disease [31].

We expected that an increased prevalence of comorbidity was associated with less aggressive treatment. A difference in comorbidity between the treatment choice groups might have been found using a different comorbidity index. An earlier study from our group in women with ovarian cancer showed that both age (≥70 years) and severe comorbidity assessed by the ASA classification (ASA score ≥3) was independently predictive of not undergoing surgery or receiving standard combination chemotherapy (carboplatin and paclitaxel) [6]. In this context, it should be noted that the tendency was that younger patients with ovarian cancer received monotherapy only in cases of a poor PS, while carboplatin monotherapy is frequently chosen in older patients because of high age alone [6]. The ASA classification is strongly based on functional status such as PS, which may explain its predictive value in this study.

A previous study conducted in 11,139 patients with ovarian cancer showed that the impact of comorbidity was most pronounced in subgroups, where the overall cancer mortality is lower, such as patients with less aggressive cancer and younger patients [32]. Read et al. [33] also came to the conclusion that comorbidities had the greatest impact among groups with higher survival rates in a population of patients with various cancer diagnoses. This may also partly explain the findings from our older cancer population.

Different comorbidities may also affect outcomes differently, as in the case of the study of patients with endometrial cancer referred to earlier [31]. We found a relatively high prevalence of both mild-to-moderate and severe comorbidity in the curative treatment choice group. It is possible that patients with comorbid conditions might have a better chance of early detection of their malignant disease, simply because of their increased contact with physicians and hospitals and a resulting increase in examinations. This hypothesis is supported by a study, which found that comorbidity burden was associated with higher rates of mammography and an earlier stage at diagnosis in patients with breast cancer [34]. Although it has been argued that comorbidity can mask early cancer symptoms, most studies have found a higher prevalence of comorbidity in patients with early-stage cancer. This association seems, however, to be dependent on the specific comorbid condition [35]. As mentioned earlier, the lack of associations between the CCI and cancer-specific and all-cause mortality could be owing to the treatment choice primarily being based on the oncologist's assessment of PS and FIGO. It is also possible that comorbidities were managed well enough not to influence mortality in this population.

As the NPR only includes information about contacts/discharges from non-psychiatric hospitals, emergency rooms, and outpatient visits, it is possible that milder cases of certain conditions such as diabetes mellitus and chronic pulmonary disease are underreported in this study, as these are usually treated by general practitioners in Denmark. A previous study has, however, found the accuracy of NPR coding of CCI comorbidities consistently high [36]. As proposed in the meta-analysis by Jiao et al. [28], underreporting of comorbidity would bias the association between comorbidity and survival toward the null value. We only assessed non-malignant comorbidity, which may also contribute to an underestimation of comorbidity. During the reviewing of the pathology results, we did not find an indication of synchronous cancer in this population, and we know that they did not receive another gynecological cancer diagnosis during the study period.

The strength of the Danish Causes of Death Register is its completeness, but the database contains a limitation in that it is the physician on call at the time of death who registers the cause of death, which means that it is not necessarily a physician who is familiar with the medical history. This may compromise the validity of the cause of death registration.

Another limitation of this study is the low number of patients in some strata, which could have impacted some of the results and explains some surprising findings, such as only a PS of 4 was found to impact survival, when it is well established that PS is a significant prognostic factor. Most of the patients with a missing FIGO stage had endometrial cancer. The majority (approximately 70%) of patients with endometrial cancer with a missing stage received curative intended treatment, indicating that they had low-stage disease, which is in line with what would be expected in an endometrial cancer population. This indicates that the risk of systematic error as a result of a missing stage is very small.

A strength of our study is that data were derived from valid databases of surgical and pathological data, and that oncologic and other relevant data were supplemented with data from the medical charts of the patients, including double checking of the pathological diagnoses. As our population derives from a database (DGCD) that collects information on all patients diagnosed with gynecological cancer, and the data are collected prospectively, it greatly diminishes the risk of selection bias and also limits information bias from this database. We also adjusted for several clinically significant covariates in our analysis in an effort to reduce potential confounding. Our population is, furthermore, representative of the entire Danish population, as described earlier.

Previous studies have shown that optimal surgical and medical treatment of older patients with ovarian cancer is feasible [37–39]—even though more toxicity is to be expected in this group [40, 41]. There is increasing awareness on how to best manage treatment decisions in individual older patients with cancer and thereby provide personalized medicine to this complex and heterogeneous group. Extra focus on good supportive care is of particular importance in older patients with cancer. It is well known that older patients with cancer are under-represented in clinical trials and that only the fittest older patients without comorbidity are included [42]. This is a challenge in daily clinical practice because the majority of patients with cancer are older. Multidisciplinary collaboration with geriatricians in the oncological setting should be implemented in daily clinical practice because studies have indicated that a comprehensive geriatric assessment is able to predict severe treatment-related toxicity [5, 43, 44] and overall survival in different cancer diseases and treatment settings [45–47]. Furthermore, a comprehensive geriatric assessment is able to influence treatment choice and intensity [48–50].

5 Conclusion

Only a few studies have assessed factors influencing oncologic treatment decisions and survival in an older gynecological cancer population. Knowledge of how oncologic treatment decisions are made and the evidence behind the treatment of this population are sparse [51, 52]. Our study showed that in an older gynecological cancer population, age, FIGO stage, and PS, but not comorbidity, were predictors of treatment decisions. Treatment choice, FIGO stage, and PS were predictors of mortality. Age was predictive of all-cause mortality in ovarian cancer, while comorbidity was not a predictor of mortality. Thus, our study indicates that age along with stage and PS might be a much stronger factor than comorbidity when making treatment decisions in an older cancer population. This does not, however, reduce the need for a pretreatment careful evaluation (e.g. geriatric assessment), in older patients with gynecological cancer, particularly those with ovarian cancer.

Acknowledgements We thank the Danish Cancer Society and The Velux Foundation for funding the study.

Compliance with Ethical Standards

Funding The study was funded by the Danish Cancer Society and The Velux Foundation. The sponsors did not have any role in the study design, collection of data, analyses or the interpretation of results, manuscript development, or in the decision to submit the manuscript for publication.

Conflict of interest Sambavy Nadaraja, Trine Lembrecht Jørgensen, Lars-Erik Matzen and Jørn Herrstedt have no conflicts of interest that are directly relevant to the contents of this article.

References

1. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol. 2009;27(17):2758–65.
2. Ør Knudsen A, Schledermann D, Nyvang G-B, et al. Trends in gynecological cancer among elderly women in Denmark, 1980–2012. Acta Oncol. 2016;55(Suppl. 1):65–73.
3. Valderas JM, Starfield B, Sibbald B, et al. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009;7(4):357–63.

4. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
5. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29(25):3457–65.
6. Jorgensen TL, Teiblum S, Paludan M, et al. Significance of age and comorbidity on treatment modality, treatment adherence, and prognosis in elderly ovarian cancer patients. Gynecol Oncol. 2012;127(2):367–74.
7. Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. Dan Med Bull. 1997;44(4):445–8.
8. Pedersen CB. The Danish civil registration system. Scand J Public Health. 2011;39(7 Suppl.):22–5.
9. Petri AL, Kjaer SK, Christensen IJ, et al. Validation of epithelial ovarian cancer and fallopian tube cancer and ovarian borderline tumor data in the Danish Gynecological Cancer Database. Acta Obstet Gynecol Scand. 2009;88(5):536–42.
10. Helweg-Larsen K. The Danish Register of causes of death. Scand J Public Health. 2011;39(7 Suppl.):26–9.
11. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130–9.
12. Jorgensen TL, Hallas J, Friis S, et al. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. Br J Cancer. 2012;106(7):1353–60.
13. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient register. Scand J Public Health. 2011;39(7 Suppl.):30–3.
14. Extermann M. Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol. 2000;35(3):181–200.
15. Extermann M, Overcash J, Lyman GH, et al. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol. 1998;16(4):1582–7.
16. Grann AF, Thomsen RW, Jacobsen JB, et al. Comorbidity and survival of Danish ovarian cancer patients from 2000–2011: a population-based cohort study. Clin Epidemiol. 2013;5(Suppl. 1):57–63.
17. Sperling C, Noer MC, Christensen IJ, et al. Comorbidity is an independent prognostic factor for the survival of ovarian cancer: a Danish register-based cohort study from a clinical database. Gynecol Oncol. 2013;129(1):97–102.
18. Du Bois A, Rochon J, Lamparter C, et al. Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. Int J Gynecol Cancer. 2005;15(2):183–91.
19. O'Malley CD, Cress RD, Campleman SL, et al. Survival of Californian women with epithelial ovarian cancer, 1994–1996: a population-based study. Gynecol Oncol. 2003;91(3):608–15.
20. Fago-Olsen CL, Hogdall C, Kehlet H, et al. Centralized treatment of advanced stages of ovarian cancer improves survival: a nationwide Danish survey. Acta Obstet Gynecol Scand. 2011;90(3):273–9.
21. Tetsche MS, Dethlefsen C, Pedersen L, et al. The impact of comorbidity and stage on ovarian cancer mortality: a nationwide Danish cohort study. BMC Cancer. 2008;8:31.
22. Tetsche MS, Norgaard M, Jacobsen J, et al. Comorbidity and ovarian cancer survival in Denmark, 1995–2005: a population-based cohort study. Int J Gynecol Cancer. 2008;18(3):421–7.
23. Elit L, Bondy SJ, Chen Z, et al. A tale of two time periods: ovarian cancer trends in Ontario. Curr Oncol. 2007;14(2):57–60.
24. Elit LM, Bondy SJ, Paszat LP, et al. Surgical outcomes in women with ovarian cancer. Can J Surg. 2008;51(5):346–54.
25. Tingulstad S, Skjeldestad FE, Halvorsen TB, et al. Survival and prognostic factors in patients with ovarian cancer. Obstet Gynecol. 2003;101(5 Pt 1):885–91.
26. Maas HA, Kruitwagen RF, Lemmens VE, et al. The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study. Gynecol Oncol. 2005;97(1):104–9.
27. DiSilvestro P, Peipert JF, Hogan JW, et al. Prognostic value of clinical variables in ovarian cancer. J Clin Epidemiol. 1997;50(5):501–5.
28. Jiao YS, Gong TT, Wang YL, et al. Comorbidity and survival among women with ovarian cancer: evidence from prospective studies. Sci Rep. 2015;5:11720.
29. Noer MC, Sperling CD, Ottesen B, et al. Ovarian cancer and comorbidity: is poor survival explained by choice of primary treatment or system delay? Int J Gynecol Cancer. 2017;27(6):1123–33.
30. Janssen-Heijnen ML, Maas HA, Houterman S, et al. Comorbidity in older surgical cancer patients: influence on patient care and outcome. Eur J Cancer. 2007;43(15):2179–93.
31. Boll D, Verhoeven RH, van der Aa MA, et al. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995–2008. Eur J Cancer. 2011;47(10):1504–10.
32. Stalberg K, Svensson T, Lonn S, et al. The influence of comorbidity on mortality in ovarian cancer patients. Gynecol Oncol. 2014;133(2):298–303.
33. Read WL, Tierney RM, Page NC, et al. Differential prognostic impact of comorbidity. J Clin Oncol. 2004;22(15):3099–103.
34. Yasmeen S, Xing G, Morris C, et al. Comorbidities and mammography use interact to explain racial/ethnic disparities in breast cancer stage at diagnosis. Cancer. 2011;117(14):3252–61.
35. Sogaard M, Thomsen RW, Bossen KS, et al. The impact of comorbidity on cancer survival: a review. Clin Epidemiol. 2013;5(Suppl. 1):3–29.
36. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.
37. Susini T, Amunni G, Busi E, et al. Ovarian cancer in the elderly: feasibility of surgery and chemotherapy in 89 geriatric patients. Int J Gynecol Cancer. 2007;17(3):581–8.
38. Hilpert F, du Bois A, Greimel ER, et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged > or = 70 years with advanced ovarian cancer: a study by the AGO OVAR Germany. Ann Oncol. 2007;18(2):282–7.
39. Perri T, Katz T, Korach J, et al. Treating gynecological malignancies in elderly patients. Am J Clin Oncol. 2015;38(3):278–82.
40. Moore KN, Reid MS, Fong DN, et al. Ovarian cancer in the octogenarian: does the paradigm of aggressive cytoreductive surgery and chemotherapy still apply? Gynecol Oncol. 2008;110(2):133–9.
41. Sud S, Lai P, Zhang T, et al. Chemotherapy in the oldest old: the feasibility of delivering cytotoxic therapy to patients 80 years old and older. J Geriatr Oncol. 2015;6(5):395–400.
42. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. J Clin Oncol. 2012;30(17):2036–8.
43. Aparicio T, Jouve JL, Teillet L, et al. Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. J Clin Oncol. 2013;31(11):1464–70.
44. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012;118(13):3377–86.

45. Clough-Gorr KM, Thwin SS, Stuck AE, et al. Examining five- and ten-year survival in older women with breast cancer using cancer-specific geriatric assessment. Eur J Cancer. 2012;48(6):805–12.
46. Spina M, Balzarotti M, Uziel L, et al. Modulated chemotherapy according to modified comprehensive geriatric assessment in 100 consecutive elderly patients with diffuse large B-cell lymphoma. Oncologist. 2012;17(6):838–46.
47. Gironés R, Torregrosa D, Maestu I, et al. Comprehensive geriatric assessment (CGA) of elderly lung cancer patients: a single-center experience. J Geriatr Oncol. 2012;3(2):98–103.
48. Decoster L, Kenis C, Van Puyvelde K, et al. The influence of clinical assessment (including age) and geriatric assessment on treatment decisions in older patients with cancer. J Geriatr Oncol. 2013;4(3):235–41.
49. Caillet P, Canoui-Poitrine F, Vouriot J, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. J Clin Oncol. 2011;29(27):3636–42.
50. Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. Ann Oncol. 2013;24(5):1306–12.
51. Hurria A, Dale W, Mooney M, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol. 2014;32(24):2587–94.
52. Wedding U, Honecker F, Bokemeyer C, et al. Tolerance to chemotherapy in elderly patients with cancer. Cancer Control. 2007;14(1):44–56.