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## Management of elderly women with endometrial cancer

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## HIGHLIGHTS

- We analyzed data from population-based tumor registry to determine how elderly patients with endometrial cancer are treated.
- Elderly patients with endometrial cancer are most likely undertreated in comparison with their younger counterparts.
- The reason for this finding is more possibly the fact the indicated treatment is not recommended to the patients.

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## ABSTRACT

**Background.** Elderly women with endometrial cancer receive less therapy in comparison with their younger counterparts. The exact reason(s) for this treatment strategy remains unclear.

**Patients and methods.** We performed a multicenter, retrospective registry-based study of 1550 patients with endometrial cancer. The outcome measure was the reason for not performing the indicated treatment.

**Results.** Median follow-up was 76.8 months. A total of 1550 women were eligible for analysis: 353 (22.7%) were younger than 60 years, 521 (33.6%) 61–70 years, 515 (33.2%) 71–80 years, and 161 (10.4%) were aged 81 years old and older. Elderly women were more likely to have non-endometrioid, undifferentiated endometrial cancer at an advanced stage. Patients younger than 60 years were more likely to receive lymphadenectomy, brachytherapy, external-beam radiotherapy (EBRT) and systemic therapy compared with the group of patients aged older than 70 years. We investigated the reason why elderly women were undertreated. The rate of indicated therapies that were not recommended by the physicians proportionally increased with an increase in patient age. Interestingly, the rate of contraindications because of performance status and/or medical disease also increased proportionally with increasing patient age. Notably, in the groups of patients older than 70 years, patient refusal was a very uncommon reason for failure to perform the indicated therapy.

**Conclusions.** Elderly women with EC are more likely undertreated because the therapy was not recommended by the physicians based on performance status and medical diseases rather than patient refusal.

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## 1. Introduction

Endometrial cancer (EC) is the most common cancer in women in developed countries and predominantly affects elderly women [1]. With the ever-increasing age of our population, the proportion of elderly women with EC will proportionally increase. The standard of care for EC patients includes surgery, i.e. hysterectomy, salpingo-oophorectomy and lymphadenectomy, if indicated. Surgical treatment is completed by adjuvant radiotherapy and systemic therapy depending on the stage of disease [2]. Previous studies have shown that elderly women with EC receive less aggressive surgery and adjuvant therapy in comparison with age-matched younger counterparts [3–6]. On the other hand,

older age at diagnosis is associated with more aggressive tumor characteristics of EC, requiring more aggressive treatment strategies. The exact reason for this discrepancy remains unclear [1]. Reduced health status is an important factor in making treatment decisions. However, this may not be the only reason why elderly patients are less likely to be treated with the indicated therapy.

The aim of this study was to evaluate the patterns of treatment of elderly women with EC, to describe age-based differences and outcomes and to investigate the reasons associated with less aggressive treatment of elderly women with EC in a large retrospective cohort register study.

## 2. Patients and methods

The cancer registry of Saxony-Anhalt, a federal state of Germany, was reviewed in order to investigate all patients with EC treated

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between 2003 and 2011. This tumor registry holds information on diagnosis, age at diagnosis, tumor stage, tumor grade, lymph node status, date of diagnosis, date of disease recurrence, date of death, suggested treatment regimens and treatment regimens used [7]. Information about the date and cause of death is automatically entered into the system shortly after death. In this cohort study, we analyzed women with EC diagnosed between 2003 and 2011 in eight hospitals in Saxony-Anhalt: University Hospital Magdeburg, Harzklinikum Dorothea Christiane Erxleben, Johanniter Clinic Genthin-Stendal, HELIOS Clinic Burg, and the AMEOS Clinics in Aschersleben, Halberstadt, Haldensleben and Schönebeck. Patients were excluded if they had uterine sarcoma, second cancer or no information about therapy. Written informed consent was obtained from all patients before treatment. Patient data were recorded blinded to patient name and date of birth. In accordance with the statement of the Research and Ethical Committee of the Otto-von-Guericke University, Magdeburg, Germany additional individual consent for this analysis was not needed. The manuscript was prepared in accordance with the STROBE statement criteria [8].

The patients were stratified by age into following groups: younger than 60 years, 61–70 years, 71–80 years and older than 81 years. Clinical and pathological variables were coded according to tumor registry criteria. The risk of recurrence was classified in accordance to the actual guidelines [2] in low, intermediate and high risk. To avoid any selection bias, patients who underwent surgery prior to 2009 were restaged according to the 2009 FIGO criteria [7]. Patients were divided into three groups based on their risk of recurrence [2]. Chronological bias was excluded because the treatment standard during the investigation period remained constant and was based on actual treatment guidelines.

To avoid further selection bias regarding surgical and adjuvant treatment, a matching analysis was performed for patients with different demographic and clinical characteristics. The matching process was based on four prognostic criteria: tumor stage, tumor histology, tumor grading and ECOG performance status. The matching procedure was conducted at random and without any information about patient outcome. Furthermore the disease-specific overall survival (DSOS) was investigated. The DSOS was calculated for patients older than 70 years and was matched to their younger counterparts. The matching process was based on aforementioned prognostic criteria.

The primary outcome measure was the rate of reception of recommended treatment in the different age groups and the reason for not performing such recommended treatment. Recommended treatment is the planned treatment after diagnosis of endometrial cancer. The reasons for failing to receive the indicated treatment were obtained by the tumor registry data and were categorized as: “rejected” if the indicated treatment was declined by the patient, “contraindicated” because of reduced performance status and/or medical disease, and “not recommended” if the indicated treatment was not recommended. Of interest was the performance of lymphadenectomy, adjuvant systemic therapy and radiotherapy such as brachytherapy and/or external beam radiotherapy (EBRT). The primary outcomes were overall survival (OS) and disease-specific overall survival (DSOS) by age group. OS and DSOS were used as the primary outcome because information about a patient’s death and its cause is automatically recorded in the cancer registry via the civil registry office, leading to a minimal loss of follow-up regarding overall survival and thus keeping transfer bias to a minimum [7]. OS was defined as the time from the date of diagnosis to the date of death from any cause. DSOS was defined as the time from the date of diagnosis to the date of death from any cause. The follow-up ended with the patient’s death, last available information in the tumor registry or the last follow-up as on 15 of September 2014.

### 2.1. Statistical analysis

The trial was designed as a retrospective cohort study with high external validity. The statistical calculations were performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). Correlation of variables and the

distribution of clinical, pathological and treatment characteristics were assessed using the chi-squared test. Survival probability was studied using the Kaplan-Meier method. The equality of survival curves was tested using the log-rank test. Cox proportional hazards models were used to assess the influence of adjuvant treatment as an independent prognostic factor and to control further for confounding bias. The statistical analyses were two-sided and  $p$ -values of  $<0.05$  were considered statistically significant.

### 3. Results

Between January 2003 and December 2011, 1736 women with malignant uterine tumors were treated in the aforementioned hospitals and were eligible for analysis. The flow diagram reports the study design and the number of patients at each stage of the study (Fig. 1). Of these patients, 186 were excluded from the analysis: 95 had uterine sarcoma, 55 had no information about adjuvant therapy and 36 had second cancer. A total of 1550 women were eligible for analysis: 353 (22.7%) were younger than 60 years, 521 (33.6%) 61–70 years, 515 (33.2%) 71–80 years and 161 (10.4%) were aged 81 years old and older. The matching analysis was based on tumor stage, tumor histology, tumor grading and ECOG performance status and was performed on 472 patients (Fig. 1).

The clinical and pathological characteristics are presented in Table 1. Women older than 81 years were less likely to have early stage disease compared with women younger than 80 years. Women older than 81 years had more undifferentiated grade 3 tumors (35.3%) compared with those 71–80 years (25.1%), 61–70 years (21.7%) and younger than 60 years (16.1%) ( $p < 0.0001$ ). They also had non-endometrioid tumors more frequently (11.0%) than women 71–80 years (7.0%), 61–70 years (6.5%) and younger than 60 years (1.9%) ( $p = 0.001$ ). The risk of recurrence increased proportionally with patient age. Women younger than 60 years were more likely to be classified with a low risk of recurrence (62.4%) and women older than 81 years were predominantly classified to have high risk of recurrence (45.3%) ( $p < 0.0001$ ). Women older than 71 years had a higher rate of ECOG performance status 1 compared to women younger than 70 years ( $p < 0.0001$ ). A significant increase in the rate of diabetes mellitus, hypertension and cardiovascular diseases was observed in the group of women older than 61 years ( $p < 0.0001$ ). Obesity was observed significantly more often in the group of women younger than 80 years compared to women older than 81 years ( $p < 0.0001$ ).

Treatment also differed between groups. Patients older than 81 years had abdominal surgery less frequently (83.6%) compared with patients 71–80 years (92.2%), 61–70 years (91.5%) and younger than 60 years (93.8%) ( $p = 0.003$ ). Women older than 81 years received lymphadenectomy in only 39.5% of patients compared to 57.3%, 65.5% and 67.7% in the groups of women 71–80 years, 61–70 years and younger than 60 years, respectively ( $p < 0.0001$ ). The median number of lymph nodes removed was not significantly different between groups ( $p = 0.093$ ). Women older than 81 years were more likely to receive pelvic radiation compared to those younger than 80 years. Patients older than 81 years had systemic therapy less frequently (0%) than patients 71–80 (1.7%), 61–70 years (5.8%) and younger than 60 years (6.2%) ( $p < 0.0001$ ).

Next, we investigated the age-related differences in treatment modalities using multivariate analysis including other clinical parameters (Table 2). Patients younger than 60 years were more likely to receive lymphadenectomy compared with the group of patients aged 71–80 (odds ratio [OR] 0.34, 95% CI 0.19–0.60) and older than 81 years (OR 0.16, 95% CI 0.08–0.31). Patients younger than 60 years were more likely to receive brachytherapy compared with patients aged 81 and older (OR 0.43, 95% CI 0.23–0.81) and EBRT compared with patients aged 71–80 years (OR 0.57, 95% CI 0.37–0.88) and older than 81 years (OR 0.50, 95% CI 0.28–0.89). Similar results were obtained with regard to systemic therapy. Women younger than 60 years were more likely to receive

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