Overview of the management of Elderly Patients with Endometrial Cancer

Florentin Racovitan | 261006911 Division of Experimental Medicine McGill University,

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1. Abstract English

Research Study Title:

Overview of the management of elderly patients with endometrial cancer

Background:

Endometrial cancer (EC) is the most common malignancy among gynecologic cancers in North America and developed countries.

The incidence of uterine cancer and associated mortality have been increasing and are projected to rise during the next decade [1, 2].

Because elderly patients with cancer are underrepresented in clinical trials, therapeutic guidelines are supported by data derived from younger patients.

Even though elderly women more often present with high- grade endometrial cancer, they undergo less often lymphadenectomy and adjuvant therapy when compared with younger patients [3, 4, 5, 6]. The poorer survival data in elderly patients compared with the younger ones may, in part, reflect these treatment decisions.

Objectives:

1. The primary objective is to compare the overall survival (OS), disease free survival (DFS), and cancer specific survival (CSS) in elderly women (≥ 70 years) with EC compare with younger patient (<70 years), treated at the Jewish General Hospital (JGH) between 2003 and 2020.

2. The secondary objective is to evaluate treatment patterns in women age ≥70 years and compare them with women below the age 70.

3. The third objective is to evaluate if there is a change in trend of the survival data (OS,

DFS and CSS) in elderly EC patients (≥70 years) in our study population and explore factors that correlated with these changes.

4. The fourth objective is to retrospectively classify patients with EC using the following markers to identify frailty: age ≥ 70 years, hemoglobin (Hb) < 10 mg/dl, Body Mass Index (BMI) < 20kg/m2, ECOG performance status ≥ 2, history of osteopenia or osteoporosis, depression and Charlson comorbidity score and evaluate the predictive value of these markers for OS.

Methods:

Data from 1244 patients with endometrial cancer treated at the JGH between January 01, 2003 and December 31, 2019 has been collected and analyzed.

Data Analysis:

For continuous variables, student t-test has been utilized to calculate p-values. A p-value less than 0.05 is defined as statistically significant.

To control confounding, we will perform a regression analysis using different models depending on the type of outcome. Survival curves have been generated using Kaplan-Meier graphs and compared using log-rank test. Results:

During the study period, 1244 women with ages between 28 and 93 years have been treated for EC at the JGH.

Results:

5-years OS (83% vs 95%, $p < 0.005$), 5-years DFS (82.7% vs 87.8%, $p < 0.02$), and 5-years CSS (93.2%vs 96.6% $p <0.03$), in elderly patients was lower than in the younger patients.

On the other hand, elderly patients who underwent Sentinel Lymph Node (SLN)

mapping had better DFS at 3-years compared to patients who had Lymph Node Dissection (LND) (91.8% vs 84.3%, p=0.03), but no difference was observed in OS and CSS in elderly patients, when comparing the type of lymph node procedure (LND vs SLN).

The DFS was also better in patients undergoing Robotic Surgery vs Laparotomy at 3-years (90.9% vs 81.7%, p=0.005), but again no difference was observed in OS and CSS, when comparing the type of surgical procedure (Robotic Surgery vs Laparotomy).

Logistic regression analysis showed that, in our elderly patient population, Hb, BMI and CCI correlate with 1-year OS.

Conclusion:

Despite advanced age and more comorbidities, elderly women with endometrial cancer can safely undergo Robotic Surgery similarly with younger women (<70 years). 3-years DFS was significantly better in elderly patients undergoing Robotic Surgery vs Laparotomy. Similarly, 3-year DFS was significantly better in elderly patients undergoing SLD vs LND. Interestingly, CSS for both age groups was similar in the stratified analysis based on tumor grade.

Only Hb, BMI and CCI have been associated with 1-year OS in our elderly patient population.

2. Abstract French

Titre de l'étude de recherche:

Aperçu de la prise en charge des patientes âgées atteintes de cancer de l'endomètre.

Contexte: Le cancer de l'endomètre (CE) est la malignité la plus courante parmi les

cancers gynécologiques en Amérique du Nord et dans les pays développés. L'incidence du cancer de l'utérus et la mortalité qui lui est associée augmentent et semblent continuer d'augmenter au cours de la prochaine décennie. Étant donné que les patientes âgées atteintes de cancer sont sous-représentées dans les essais cliniques, les lignes directrices thérapeutiques reposent sur des données provenant de patientes plus jeunes. Bien que les femmes âgées présentent plus souvent un cancer de l'endomètre de haut grade, elles subissent moins fréquemment une lymphadénectomie et une thérapie adjuvante que les patientes plus jeunes [3, 4, 5, 6,]. Les données de survie moins favorables chez les patientes âgées par rapport aux plus jeunes peuvent en partie refléter ces décisions thérapeutiques.

Objectifs:

1. L'objectif principal de l'étude est de comparer la survie globale, la survie sans maladie et la survie spécifique au cancer chez les femmes âgées (≥ 70 ans) atteintes de CE traitées à l'Hôpital général juif (HGJ) entre 2003 et 2020 et de les comparer aux patientes plus jeunes (< 70 ans).
2. L'objectif secondaire de l'étude est d'évaluer les schémas thérapeutiques chez les femmes âgées de ≥ 70 ans et de les comparer à celles de moins de 70 ans.
3. Le troisième objectif est d'évaluer s'il existe un changement de tendance dans les données de survie chez les patientes âgées atteintes de CE (≥ 70 ans) dans notre population d'étude et d'explorer les facteurs corrélés à ces changements.
4. Le quatrième objectif est de classifier rétrospectivement les patientes atteintes de CE en utilisant les marqueurs suivants pour identifier la fragilité : âge ≥ 70 ans, hémoglobine (Hb) < 10 mg/dl, indice de masse corporelle (IMC) < 20 kg/m2, état de

performance ECOG ≥ 2, antécédents d'ostéopénie ou d'ostéoporose, dépression et score de comorbidité de Charlson, et d'évaluer la valeur prédictive de ces marqueurs pour la survie globale.

Méthodes:

Les données de 1244 patientes atteintes de cancer de l'endomètre traitées à l'HGJ entre Janvier 01, 2003 et Décembre 31,2019 ont été collectées et analysées.

Analyse des données:

Pour les variables continues, le test t de Student a été utilisé pour calculer les valeurs de p. Une valeur de p inférieure à 0,05 est définie comme statistiquement significative. Pour contrôler les facteurs de confusion, nous effectuerons une analyse de régression en utilisant différents modèles en fonction du type de résultat. Des courbes de survie ont été générées à l'aide de graphiques Kaplan-Meier et comparées à l'aide du test du log-rank.

Résultats:

Pendant la période d'étude, 1244 femmes âgées de 28 à 93 ans ont été traitées pour un CE à l'HGJ. Résultats de survie : la survie globale à 5 ans chez les patientes âgées était inférieure à celle des patientes plus jeunes (83 % contre 95 %, $p < 0,005$). La survie sans maladie à 5 ans chez les patientes âgées était inférieure à celle des plus jeunes (82,7 % contre 87,8 %, $p < 0,02$). La survie liée au cancer à 5 ans chez les patientes plus jeunes était meilleure que chez les patientes âgées (96,6 % contre 93,2 %, $p < 0,03$). Les patientes âgées avaient une meilleure survie sans maladie à 3 ans (91,8 % contre 84,3 %, $p=0,03$), lors de l’utilisation du ganglion sentinelle comparé à la dissection lymphatique systématique, mais aucune différence n'a été observée dans la

survie globale ou la survie liée au cancer. La survie sans maladie était également meilleure chez les patientes ayant subies une chirurgie minimalement invasive par rapport à une laparotomie à 3 ans (90,9 % contre 81,7 %, p=0,005), mais aucune différence n'a été observée dans la survie globale ou la survie liée au cancer. L'analyse de régression logistique a montré que, dans notre population de patients âgés, l'Hb, l'IMC et le score de comorbidité de Charlson étaient corrélés à la survie à 1 an.

Conclusion:

Malgré leur âge avancé et leurs comorbidités, les femmes âgées atteintes de cancer de l'endomètre peuvent subir en toute sécurité une chirurgie minimalement invasive pour la chirurgie de stadification, de manière similaire aux femmes plus jeunes (< 70 ans). La survie sans maladie à 3 ans était significativement meilleure chez les patientes âgées subissant une chirurgie minimalement invasive par rapport à la laparotomie. De même, la survie sans maladie à 3 ans était significativement meilleure chez les patientes âgées lors de l’utilisation du ganglion sentinelle comparé à la dissection lymphatique systématique. Une découverte significative était que la survie liée au cancer pour les deux groupes d'âge était similaire dans l'analyse stratifiée en fonction du grade de la tumeur. Seuls l'Hb, l'IMC et le score de comorbidité de Charlson ont été associés à la survie à 1 an dans notre population de patients âgés.

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Florentin Racovitan

4. Contribution of Authors

All sections are authored by Florentin Racovitan, including all Chapters, Tables, Figures and Appendices. Thesis supervisor Dr. Walter H. Gotlieb provided editorial help on all sections.

5. List of Abbreviations

The list below defines abbreviations and acronyms that are used throughout the thesis.

Abbreviation	Meaning
aRR	Adjusted Relative Risk
ASCO	American Society of Clinical Oncology
BMI	Body Mass Index
CARG	Cancer and Ageing Research Group
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CRASH	Chemotherapy Risk Assessment Scale for High-age Patients
CSS	Cancer Specific Survival
CT	Computer Tomography
DFS	Disease Free Survival
DM	Diabetes Mellitus
EBRT	External Beam Radiation Therapy
EC	Endometrial Cancer
ECOG	Eastern Cooperative Oncology Group
FFS	Fried Frailty Score
FI	Frailty index
FIGO	International Federation of Gynecology and Obstetrics
GOC	The Society of Gynecologic Oncology of Canada
Hb	Hemoglobin
HDR-BT	High Dose Rate Brachytherapy

HR	Hazard Ratio
HRQOL	Health Related Quality of Life
IADL	Instrumental Activities of Daily Living
JA-ACG	Johns Hopkins Adjusted Clinical Groups
JGH	Jewish General Hospital
KPS	Karnofsky Performance Status
LFFS	Local Failure Free Survival
LND	Lymph Node Dissection
LBG-IUS	Levonorgestrel Intrauterine System
MBI	Modified Barthel Index
MIS	Minimally Invasive Surgery
MNA	Mini Nutritional Assessment
MRI	Magnetic Resonance Imaging
MSE	Mental Status Examination
NCCN	National Comprehensive Cancer Network
OR	Odds Ratio
OS	Overall Survival
PET	Positron Emission Tomography
REB	Review Ethics Board
RecR	Recurrence Risk
RR	Relative Risk
RT	Radio Therapy
SLN	Sentinel Lymph Node

VBT Vaginal Brachytherapy

VES 13 Vulnerable Elders Survey

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7. Introduction

7.1 Rational

Endometrial cancer is the most common gynecologic malignancy in the western world and the sixth most common cancer in women globally, with 382,069 new cases reported in 2018 and 89,929 deaths worldwide (Figure 1). [7]

Figure 1. Bar Chart of Incidence and Mortality Age- Standardized Rates

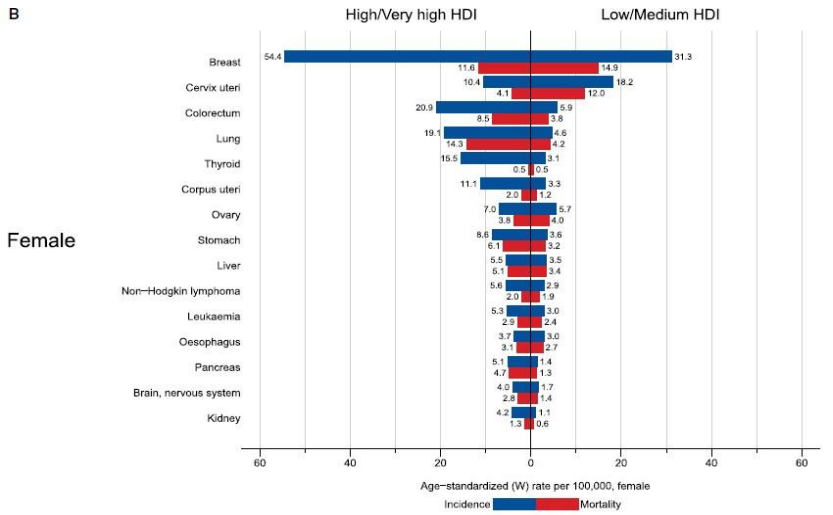


FIGURE 7. Bar Charts of Incidence and Mortality Age-Standardized Rates in High/Very-High Human Development Index (HDI) Regions Versus Low/Medium HDI Regions Among (A) Men and (B) Women in 2018. The 15 most common cancers world (W) in 2018 are shown in descending order of the overall age-standardized rate for both sexes combined. Source: GLOBOCAN 2018.

With the increased life expectancy, the numbers of patients diagnosed and surviving endometrial cancer increases as well.

In North America, the incidence of uterine cancer and associated mortality have been increasing and are projected to rise during the next decade [2, 8]. Some of the risk factors responsible for this are the increasing rates of obesity, early menarche, late menopause, nulliparity and aging population [8].

An estimated 8,100 Canadian women have been diagnosed with uterine cancer in 2022. An estimated 1,500 will die from the disease. In Canada, the 5-year net survival

for uterine cancer is 82%. This means that about 82% of women diagnosed with uterine cancer will survive for at least 5 years [8].

Because elderly patients with cancer are underrepresented in clinical trials, therapeutic guidelines are supported by data derived from younger patients. It is believed that the established standard treatment cannot be offered to elderly patients because of the presence of multiple comorbidities and frailty.

Even though elderly women more often present with high- grade endometrial cancer, they undergo less often lymphadenectomy and adjuvant therapy when compared with younger patients [3, 4, 5, 6]. The poorer survival data in elderly patients compared with the younger ones may, in part, reflect these treatment decisions.

As such, it is important to investigate the treatment pattern of women with endometrial cancer age ≥70 years, compare it with the ones younger than 70 and evaluate the impact on survival.

A retrospective chart review of patients with endometrial cancer treated at the Jewish General Hospital between January 01, 2003, and December 31, 2019, was conducted with the intention of analyzing survival data and treatment pattern in women age ≥70 years and compare with women below the age of 70.

7.2. Objectives

The primary objective of the study was to compare the overall survival (OS), disease free survival (DFS), and cancer specific survival (CSS) in elderly women (≥ 70 years) with endometrial cancer treated at Jewish General Hospital between 2003 and 2020 and compare with younger patient (<70 years) treated at JGH during the same period.

The secondary objective was to evaluate treatment patterns (based on age, BMI, comorbidities, histological type, FIGO stage, type of surgery, chemotherapy, and radiotherapy) in women age ≥70 years and compare with women below the age 70.
The third objective was to evaluate if there is a change in trend of the survival data (OS, DFS and CSS) in elderly patients (≥70 years) treated at JGH between 2003 and 2020 and explore factors that correlated with these changes.
The fourth objective was to retrospectively classify patients with endometrial cancer using the following markers to identify frailty: age ≥ 70 years, albumin <35 g/dl, hemoglobin < 10 mg/dl, BMI < 20kg/m2, ECOG performance status ≥ 2, history of osteopenia or osteoporosis, Depression and Charlson comorbidity index (CCI), and using logarithmic regression analysis to evaluate the predictive value of these markers for OS.

7.3. Hypothesis

We hypothesize there will be a difference in treatment patterns in women above the age 70 and that DFS and CSS will be different in women with endometrial cancer 70 years and older compared to women below the age 70.
We hypothesize that there will be a trend over time, maybe reflecting better decision making based on the reduced morbidity of sentinel lymph node mapping resulting in better OS, DFS, CSS in women over 70 years compared with the era prior to sentinel lymph node.
Finally, we hypothesize that frailty markers are associated with patient survival and can be used to better guide treatment decisions in elderly patients with endometrial cancer.

8. Comprehensive review of the relevant literature

A. Management and survival of elderly patients with endometrial cancer.

The primary treatment for localized disease is total hysterectomy with bilateral salpingo-oophorectomy and surgical staging [8].

Surgery represents a challenge since elderly patients often present with multiple comorbidities and poor performance status. Management of these patients often rely on expert opinions because they are underrepresented in clinical trials. Elderly patients (> 80 years) presented more often with worse disease including high-grade endometrial cancer: 48% vs 37% (p=0.003) and Lymphovascular Space Invasion (LVSI): 55% vs 29% (<0.001) compared with the younger patients (≤ 65 years) [3].

Elderly women also underwent less often lymphadenectomy and adjuvant treatment [3, 4, 5, 6, 9], including brachytherapy, EBRT, and systemic therapy (Table 3) [10]. After matching for tumor stage, tumor histology, tumor grade, and ECOG PS, overall survival (OS) of patients 70 years and over was significantly lower compared to the younger population (10-years OS: 81.4% (<60 y), 64.4% (61-70y), 44.1% (71-80y), and 42.4% (≥ 81 y)) (Figure 2) [11].

Figure 2. Overall Survival for Women with Endometrial Cancer A) In function of patient age; B) After matching for Tumor Stage, Tumor Histology, Tumor Grading and ECOG Performance status.

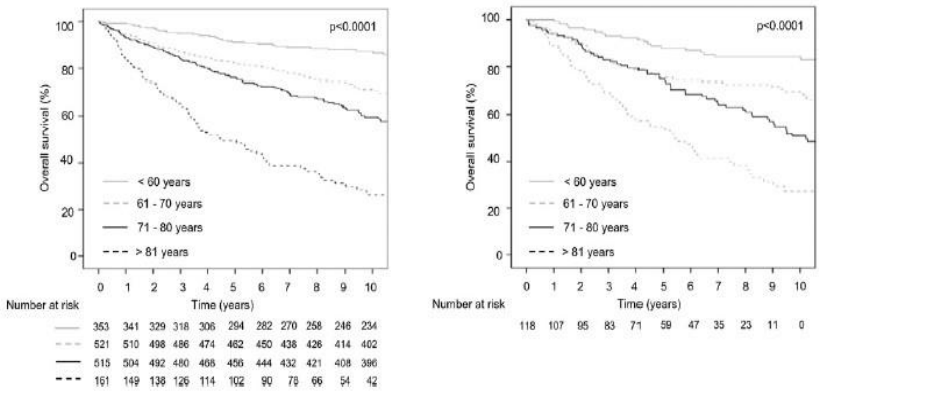


Fig. 2. Overall survival for women with endometrial cancer. A) depending on patient age; B) after matching for tumor stage, tumor histology, tumor grading and ECOG performance status. ECOG, Eastern Cooperative Oncology Group.

The most common reasons why therapy was not recommended in the elderly patients (>60y) were contraindications due to comorbidities or poor performance status.

In conclusion, lower Cancer Specific Survival (CSS) observed in the elderly patients with endometrial cancer is in part due to the increased rate of high-grade EC in the elderly population and also because of “undertreatment” [3].

B. Surgical management and survival in elderly patients with endometrial cancer.

Laparotomy, the traditional surgical approach, has been progressively replaced with Robotic Surgery because of reduced postoperative complications and faster recovery time [6, 9, 12, 13, 14]. Some reluctance exists in performing Robotic Surgery in elderly patients with cardio-pulmonary comorbidities due to potential negative effect of prolonged Trendelenburg position.

When comparing the surgical approach in the elderly, robotic surgery resulted in lower rates of medical and surgical postoperative complications than laparotomy [15].

A study from our group published in 2015 showed that patients undergoing robotic surgery for EC had similar complications regardless of age groups [12].

In conclusion, elderly patients benefit from robotic surgery.

C. Radiotherapy as an adjuvant and in palliative setting in elderly patients with endometrial cancer.

Adjuvant radiotherapy is often planned for patients with endometrial cancer after surgery. Radiotherapy can be administered as external beam radiotherapy (EBRT), brachytherapy (BT), or combinations of both.

Elderly patients often do not receive the standard of care for radiotherapy [17], despite studies showing that radiotherapy is feasible and well tolerated even in nonagenarian patients with gynecologic malignancy [18].

D. Hormonal treatment in palliative setting for inoperable elderly patients with endometrial cancer.

Several retrospective studies have shown that hormonal therapy represents an alternative for post-menopausal women that are unable to undergo surgery for endometrial cancer.

Studies included Levonorgestrel intrauterine system (LNG-IUS) [19], and Anastrozole with acceptable responses [20].

E. Comprehensive Geriatric Assessment (CGA) in elderly patients with endometrial cancer.

An important distinction needs to be made between a patient's chronologic age and physiological and functional status. Performing a CGA can reveal previously unidentified health problems, predict tolerance to adjuvant treatment and life expectancy of the patient. Several screening tools have been developed over the years to identify patients at risk that would benefit from a CGA.

An important prognostic factor for elderly patients with cancer is the health-related

quality of life (HRQOL) [22]. Scales exist for assessing chemotherapy toxicity risk in oncologic patients, either CARG (Cancer Aging Research Group) or CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) tools [23].

The G8 has been specifically developed in oncology and consists of eight items allowing to identify elderly cancer patients who could benefit from CGA [21].

A systematic review of 35 studies has shown that CGA is able to affect oncologic treatment decisions, leading to modification in initial treatment plan in 28% of the patients [28].

F. Frailty in elderly patients with endometrial cancer.

The need for a standardized and effective frailty assessment in elderly patients is evident. Frailty, a condition characterized by a reduced capacity to cope with health stressors, isn't exclusive to the elderly but is more prevalent among them. However, the prevalence of frailty can vary significantly depending on the definition and scoring system used. Without a consistent way to evaluate frailty, various models have been proposed to predict negative health outcomes in patients, such as those with endometrial cancer. These models utilize different criteria, including laboratory values, performance status, or specific frailty indicators. Finding a reliable frailty score for the elderly is crucial, as it has been shown to be a significant predictor of outcomes like recurrence, complications, and mortality in this population, emphasizing the importance of implementing a consistent and effective frailty assessment tool.

The heterogeneity of the frailty marker included in various models: physical limitations in preforming various activities, laboratory values, health deficits as well as the number of the variables included in each scoring system, explains the poor correlation between

them [29, 30, 31, 32, 35].

Stressors like surgery, adjuvant chemotherapy and radiotherapy can precipitate negative health outcomes in vulnerable patients, identifying frailty as soon as possible could potentially improve patient outcomes. The CGA represents the gold standard for evaluating the functional and health status of elderly patients but is often not routinely included in the initial evaluation of cancer patients [36]. More prospective studies evaluating the effectiveness of screening tools to predict negative health outcomes in elderly patients with endometrial cancer are needed [31, 33, 34].

9. Body of the thesis

9.1. Methodology

Patients

Demographic and clinical data of patients with endometrial cancer treated at the Jewish General Hospital between January 01, 2003 and December 31, 2010 was collected retrospectively. After December 2010 data was prospectively gathered in robotic surgical databases from electronic hospital charts. The protocol of the study has been approved by the Institution Review Ethics Board (protocol # 2022-3038).

Women with uterine sarcoma, two primary tumors, prophylactic hysterectomy and surgical staging in another institution were excluded.

Data collected

The following information was collected: patient's age at the time of surgery, date of surgery, body mass index (BMI), preoperative histology and tumor grade, tumor histology and tumor grade based on final pathology, disease stage, type of lymph node

sampling (sentinel lymph node mapping (SLN) or lymph node dissection (LND)), lymph node count and metastases, use of adjuvant therapy (chemotherapy and/or radiotherapy), recurrence information, pre-operative albumin level, pre-operative hemoglobin level, comorbidities, ECOG performance status, follow-up time, and survival information (date and cause of death).

Staging and histology

For the initial evaluation, all patients underwent a history and physical examination, endometrial biopsy or dilatation and curettage. Depending on the initial findings, other investigations like computer tomography (CT) scan, magnetic resonance imaging (MRI) or positron emission tomography (PET) scan were requested as needed.

All patients have been classified according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification after final pathological report. Grading of the tumors was decided based on the percentage of cells that grow in sheets (solid tumor growth) rather than from glands: grade 1(less than 5%), grade 2 (between 6- 50%) and grade 3(>50%) [8].

Treatment and follow-up

Initial treatment for patients with disease limited to the uterus is total hysterectomy, bilateral salpingo-oophorectomy, and surgical staging.

Between January 2003 and November 2010 all endometrial cancer patients underwent complete pelvic lymph node dissection with paraaortic lymphadenectomy depending on established risk factors, as part of the surgical staging, in line with GOC guidelines. Between December 2010 and September 2014, all patients underwent SLN mapping as well as completion pelvic lymph node dissection and para- aortic lymphadenectomy in

selected high-grade cancers.

After this period, until the end of the study period, all patients underwent the NCCN SLN protocol [37]. Throughout the study period, para-aortic LND was selectively performed in patients with either positive pelvic LN or grade 3 tumors.

Endometrial cancer patients were followed every 4 months for the first 2 years post treatment, then every 6 months until 5 years post treatment, and yearly thereafter. The last follow-up appointment evaluated for this study was September 2022.

Data analysis

For descriptive statistics we used mean ± standard deviation (SD) and median, when appropriate. Frequencies have been reported as percentage. Patient characteristics and demographic data for the two groups of patients has been compared for statistical significance using t-test (for continuous variables) and Fisher exact test when indicated (less than 5 observations in either group). Kaplan Meier survival curves have been calculated using the following definitions for OS, DFS and CSS.

Overall survival (OS) was defined as time from surgery to time of death due to any causes (measured in months).

Disease free survival (DFS) has been calculated from the time of surgery to the time of disease recurrence or death from any cause.

Cancer specific survival (CSS) has been defined as the length of time from surgery to the date of death due to cancer.

Disease recurrence was diagnosed by imaging studies or biopsy.

Patients in palliative care without a confirmed date of death have been censored at last date of follow-up.

The difference between survival curves has been compared with the log-rank test. A p-value of < 0.05 was considered statistically significant. P values will be reported at three decimal places. If the p value is less than 0.001 it will be reported as $p < 0.001$.
Data was collected in Excel and the analysis was done using R 1.4.1717.

9.2. Results:

During the study period, 1216 patients with endometrial cancer have been treated at the JGH. 798 (66%) patients were below 70 years, and 418(34%) patients were ≥70 years. The mean age at diagnosis for the entire study population was 64.89 years (range: 28-93), with the mean age 58.52y (28-69) and 77.04y (range: 70-93) for the younger and elderly cohort, respectively. BMI for the entire study population was 32.34 (±8.9) kg/m2, with 33.15 (±9.49) kg/m2 and 30.76 (±7.36) kg/m2 for the group < 70y and >70y respectively (Table 1.).

Most patients (77.55%) presented with endometrioid adenocarcinoma; A higher proportion of patients in the younger group compared with the elderly group presented with this histology (82.58% vs 67.94%, $p < 0.001$). Papillary serous carcinoma was documented more often in the elderly group (>70y) compared with the younger group (<70y): 17.94% vs 9.39% ($p < 0.001$). Carcinosarcoma was reported more often in the elderly group compared with the younger ones: 7.18% vs 2.26% ($p < 0.001$) (Table 1.). Grade 1 histology have been documented more often in the younger group (<70y) compared with the elderly ones (>70y): 46.99% vs 25.84% ($p< 0.001$). More patients in the elderly group (>70y) compared with the younger ones (<70y) presented with grade 3 histology: 45.21% vs 22.93% ($p < 0.001$). A similar percentage of patients in the two

age groups had grade 2 histology: 30.08% vs 28.95% (p = 0.731). Most patients (53.06%) presented at diagnosis with IA FIGO stage. A higher proportion of patients presented at diagnosis with IA FIGO stage in the younger group (<70y) compared with the elderly group (>70y): 58.19% vs 43.27% (p < 0.001). More patients in the elderly group had stage II FIGO at presentation compared to younger ones: 8.41% vs 4.4% (p < 0.006). Elderly patients (>70y) had more often FIGO stage IIIC at presentation that the younger cohort (<70y): 16.83% vs 9.7% (p < 0.001) (Table 1.).

A minority of women (3.27%) were diagnosed with FIGO stage IV disease, with 2.77% (22) and 4.33% (18) of women from the <70y group and >70y group, respectively.

The mean number of comorbidities was 2.27 (± 1.94 SD) for the entire study population, elderly patients presenting on average with significantly more comorbidities (p < 0.001) that the younger ones (3.08 ± 2.17 vs 1.85 ± 1.66). Similarly, the mean number of medications was significantly higher (p < 0.001) in the elderly group compared to the younger one (4.17 ± 2.99 vs 2.47 ± 2.46) (Table 1).

Overall, the elder patients presented with more aggressive and more advanced disease than the younger population.

Table 1. Descriptive Statistics of the Study Population

	All ages	Age < 70	Age ≥ 70	P value
N (%)	1216	798 (66%)	418 (34%)	
Follow-up Time: mean, SD (months)	67.46 ± 49.33	72.88 ± 51.07	57.2 ± 44.12	< 0.001
Age (years) mean(min-max)	64.89 (28-93)	58.52 (28-69)	77.04(70-93)	< 0.001
BMI (mean)	32.34 ± 8.9	33.15 ± 9.49	30.76 ± 7.36	< 0.001
Histology n (%)				
Endometrioid adenocarcinoma	943(77.55%)	659(82.58%)	284(67.94%)	< 0.001
Papillary serous carcinoma	150(12.33%)	75(9.39%)	75(17.94%)	< 0.001
Clear cell carcinoma	43(3.54%)	24(3%)	19(4.55%)	0.224
Carcinosarcoma	48(3.95%)	18(2.26%)	30(7.18%)	< 0.001
Adenosquamous carcinoma	21(1.73%)	13(1.63%)	8(1.91%)	0.896
Others (Carcinoma)	11(0.9%)	9(1.13%)	2(0.48%)	0.348

Grade 1	483(39.72%)	375(46.99%)	108(25.84%)	< 0.001
2	361(29.69%)	240(30.08%)	121(28.95%)	0.731
3	372(30.59%)	183(22.93%)	189(45.21%)	< 0.001
FIGO stage: IA	642(53.06%)	462(58.19%)	180(43.27%)	< 0.001
IB	262(21.65%)	164(20.65%)	98(23.56%)	0.275
II	70(5.79%)	35(4.4%)	35(8.41%)	< 0.05
IIIA	42(3.47%)	31(3.9%)	11(2.64%)	0.331
IIIB	7(0.58%)	3(0.38%)	4(0.96%)	0.191
IIIC	147(12.15%)	77(9.7%)	70(16.83%)	< 0.001
IVA	22(1.82%)	9(1.13%)	13(3.125%)	0.025
IVB	18(1.45%)	13(1.64%)	5(1.2%)	0.730
Comorbidities	2.27 ± 1.94	1.85 ± 1.66	3.08 ± 2.17	< 0.001
HTN	611(50.25%)	323(40.48%)	288(68.9%)	< 0.001
CVD	165(13.57%)	60(7.52%)	105(25.12%)	< 0.001
CVA	37(3.04%)	15(1.88%)	22(5.26%)	< 0.01
DM	239(19.65%)	127(15.91%)	112(26.8%)	< 0.001
Chronic Resp.	143(11.76%)	95(11.9%)	48(11.48%)	0.902
GI	122(10.03%)	59(7.39%)	63(15.07%)	< 0.001

Survival results

The mean follow-up time for the entire study population was 67.46 (± 49.33) months,

with 72.88(± 51.07) and 57.2(± 44.12) months for the <70y group and > 70y group, respectively (Table 1.).

Table 2. OS for the entire study population and for the two age groups

	Entire study population	Age < 70 y	Age ≥ 70 Y	P
1-year OS	97.2%, CI: 0.962-0.982	98.5%, CI: 0.977-0.994	94.6%, CI: 0.924-0.969	
3-years OS	92.6%, CI: 0.910-0.942	95.3%, CI: 0.937-0.969	87.3%, CI: 0.839-0.908	
5-years OS	89.8%, CI: 0.879-0.917	92.8%, CI: 0.908-0.949	83.6%, CI: 0.796-0.878	< 0.001

Figure 3. OS Kaplan Meier survival curve for entire study population

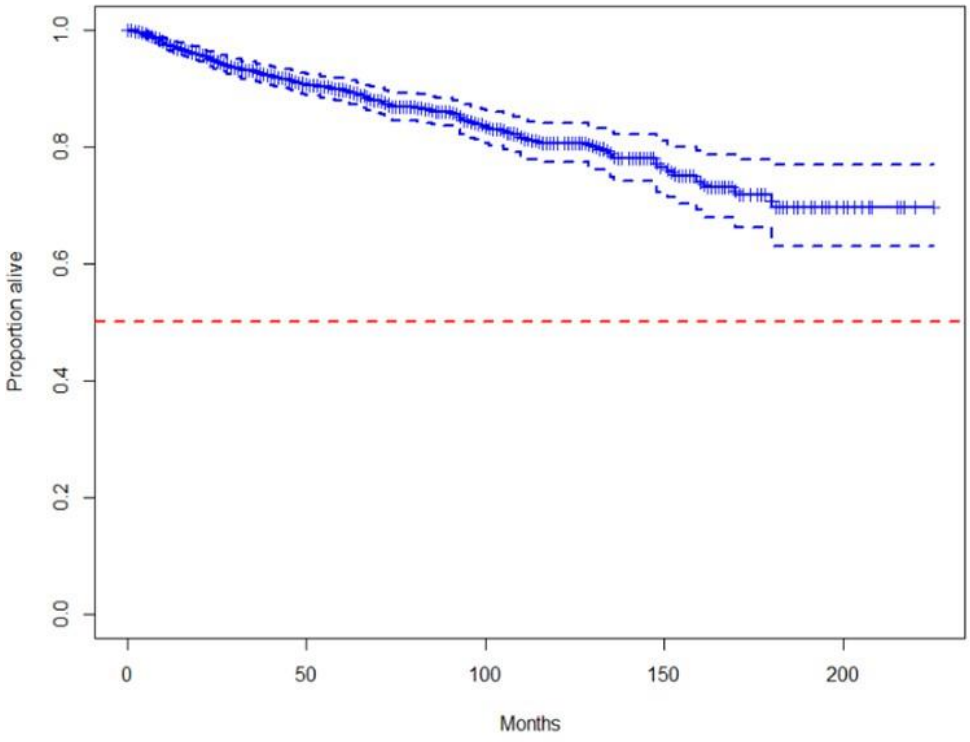


Figure 4. OS Kaplan Meier survival curves for the two age group

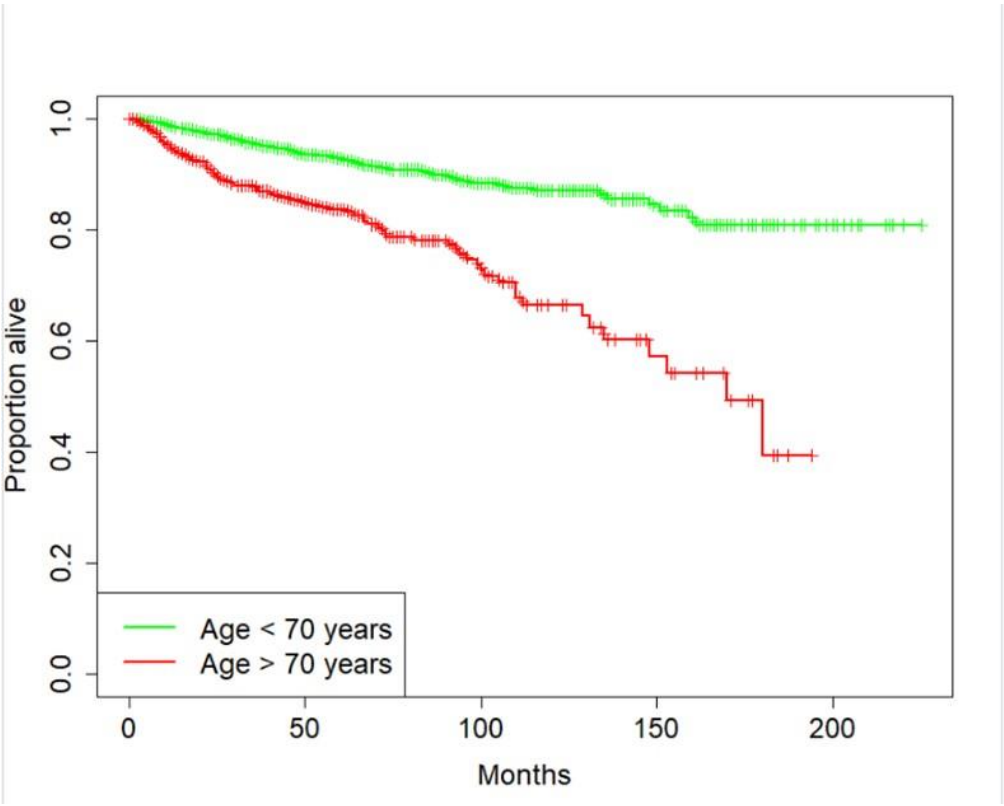


Table 3. DFS for the entire study population and for the two age groups

	Entire study population	Age < 70 y	Age ≥ 70 y	P
1-year DFS	93.7%, CI: 0.923-0.952	95.1%, CI: 0.936-0.967	91.1%, CI: 0.884-0.940	
3-years DFS	85.4%, CI: 0.833-0.875	89.6%, CI:0.874-0.919	77.1%, CI: 0.729-0.816	
5-years DFS	82.5, CI: 0.802-0.849	86.7%, CI: 0.841-0.894	74.3%, CI: 0.697-0.791	< 0.001

Figure 5. DFS Kaplan Meier survival curve for entire study population

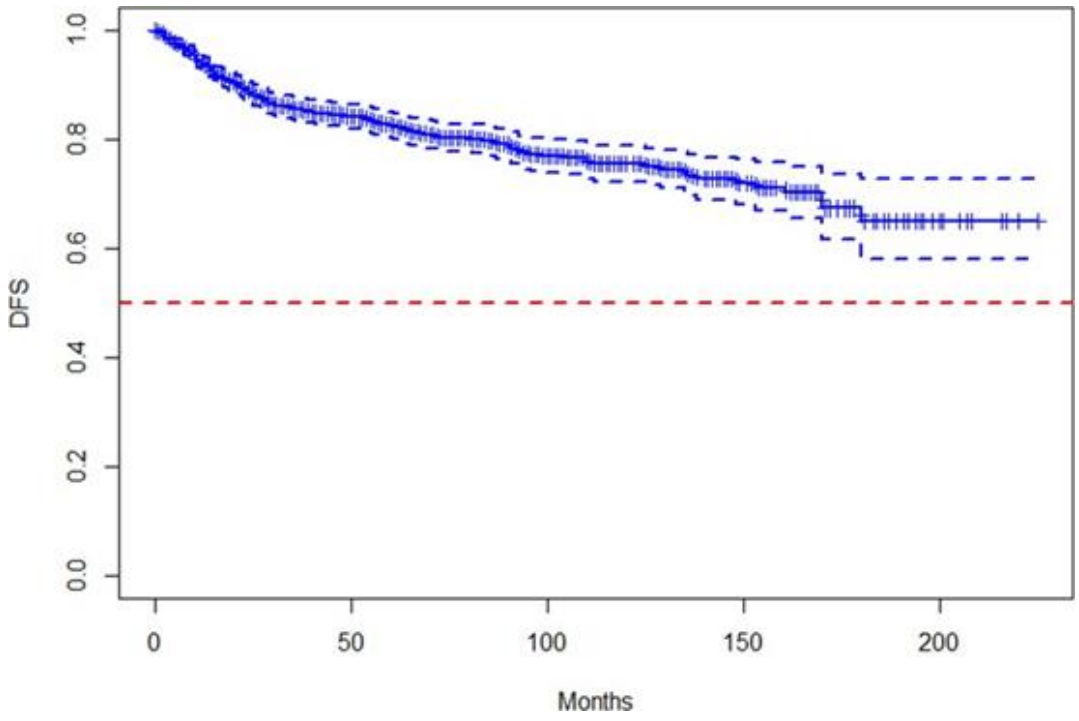


Figure 6. DFS Kaplan Meyer survival curve for the two age groups

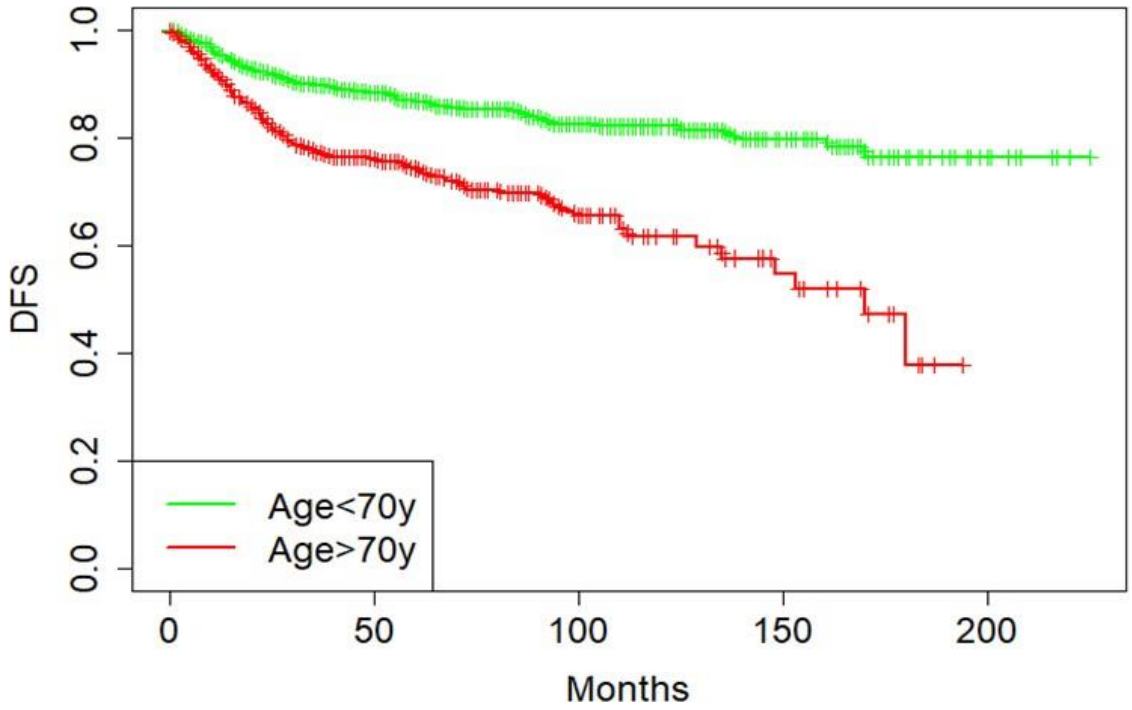


Table 4. Cancer Specific Survival (CSS) for the two age groups

	Entire study population	Age < 70 y	Age ≥ 70 Y	p
1-year CSS	98.8%, CI: 0.980-0.996	98.8%, CI: 0.980-0.996	95.6%, CI: 0.936-0.977	
3-years CSS	93.7%, CI: 0.923-0.952	95.7%, CI: 0.942-0.972	89.9%, CI: 0.867-0.931	
5-years CSS	91.6%, CI: 0.898-0.934	93.4%, CI: 0.915-0.954	87.9%, CI: 0.845-0.915	p = 0.005

Figure 7. CSS Kaplan Meier survival curve for entire study population.

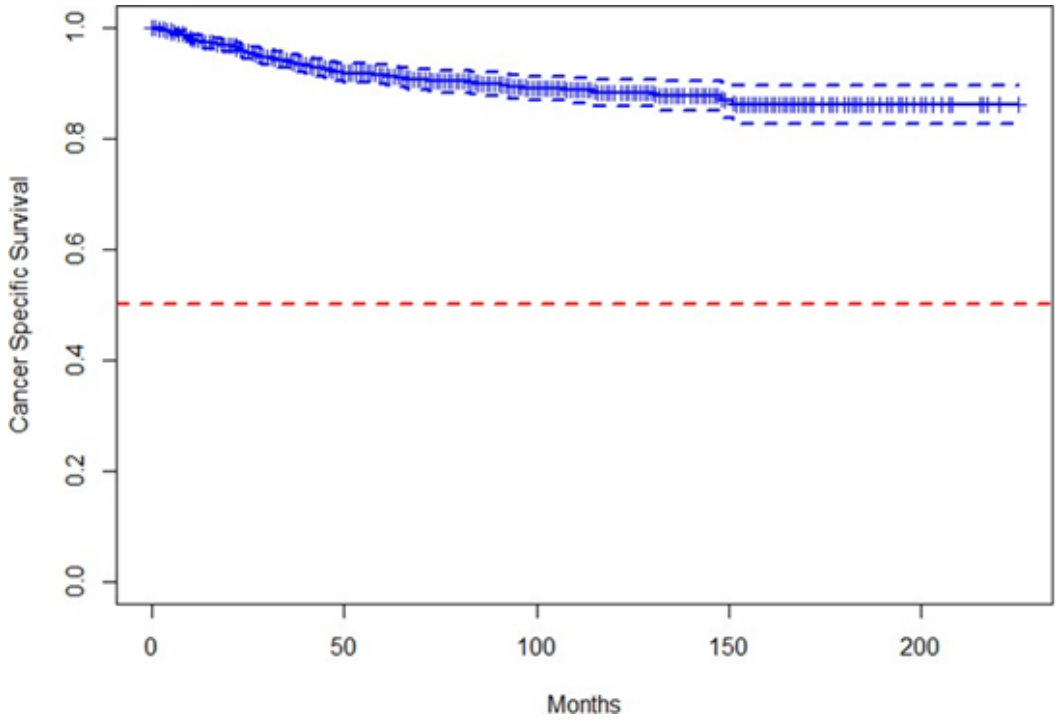
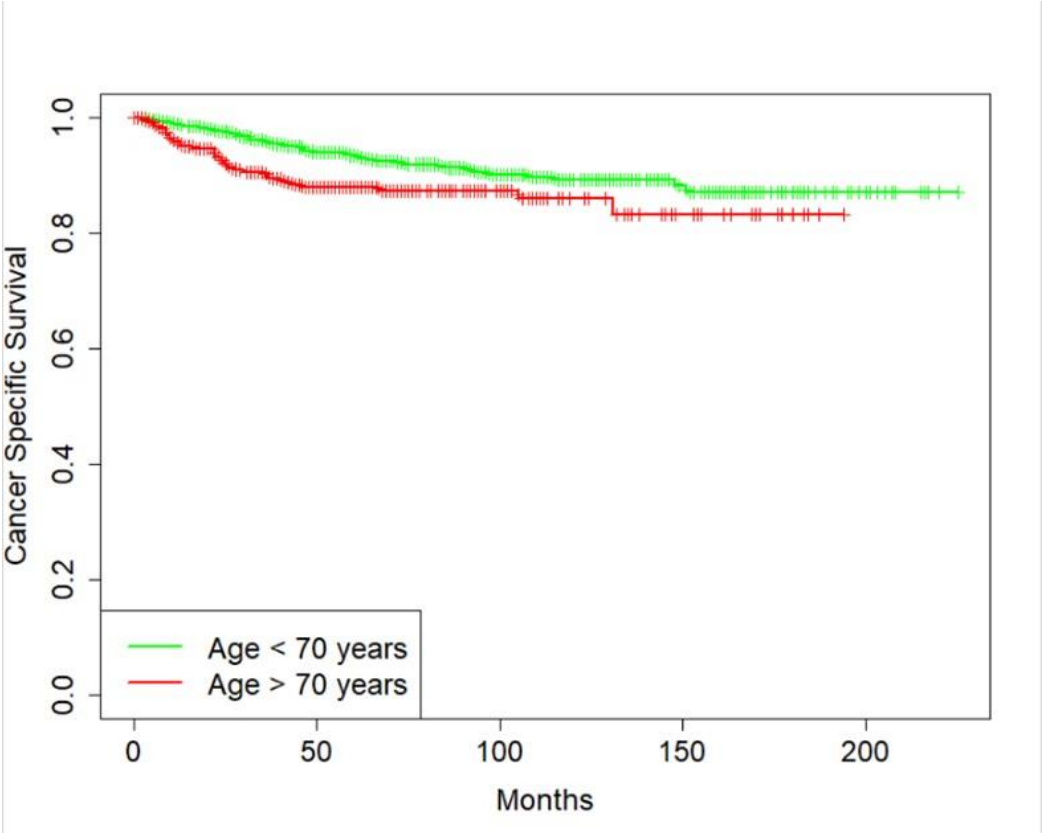


Figure 8. CSS Kaplan Meier survival curves for the two age groups.



Second objective results:

Most patients (82.15%) underwent Robotic Surgery.

Table 5. Type of Surgery and Adjuvant Therapy for the Two Age Groups

	All ages	< 70 y	>70y	p-value
Type of surgery* Laparotomy	215(17.68)	127(15.91)	88(21.05%)	< 0.05
Robotic Surgery	999(82.15%)	670(83.96%)	329(78.7%)	0.028
Chemotherapy	358(29.44%)	207(25.94%)	151(36.12%)	< 0.001
Radiotherapy	502(41.28%)	297(37.22%)	205(49.04%)	< 0.001

Patients in the younger group received more often Robotic Surgery compared with the

elderly patients: 83.96% vs 78.7% (p = 0.028) (Table 5.).

Patients in the elderly group underwent more often laparotomy compared with the younger age group: 21.05% vs 15.91% (p < 0.005) (Table 5.).

With the introduction of Robotic Surgery in 2008, the numbers of patients with endometrial cancer undergoing traditional laparotomy decreased quickly over the following years, with robotically assisted surgery becoming the main type of surgical procedure regardless of the patients' age (Table 5.).

Figure 9. Type of surgical procedure in patients < 70 years between 2003 - 2019

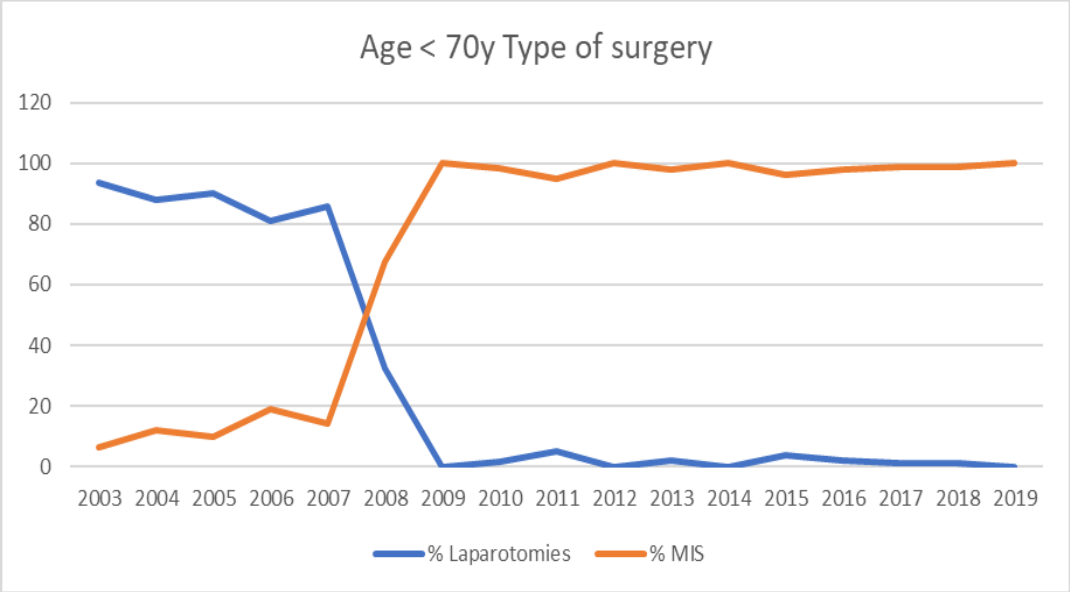
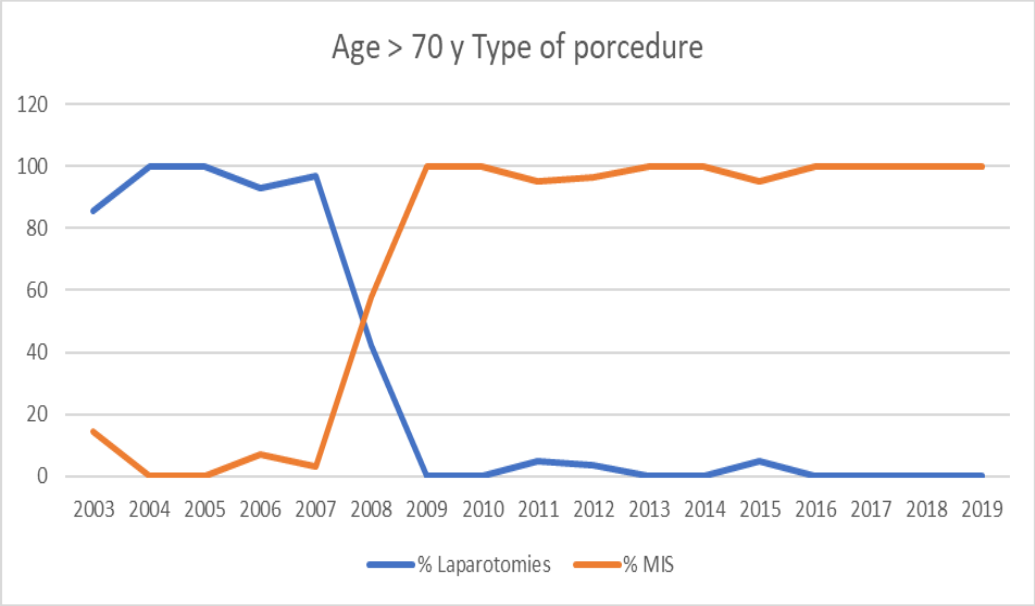


Figure 10. Type of surgical procedure for patients > 70 years between 2003-2019



Before the introduction of SLN mapping (December 2010), the mean number of LN sampled was significantly higher (p = 0.005) in the younger women, compared with elderly women (11.34 ± 5.59 vs 9.3 ± 5.36). No statistically significant difference in the number of lymph nodes was noted between the two age groups after December 2010. 29.44% (358) of women with EC received chemotherapy. Patients in the elderly group received more often chemotherapy compared with the younger ones: 36.12% vs 25.94% (p < 0.001). 41.28% (502) patients of the entire study population received radiotherapy.

Patients in the elderly group received more often radiotherapy compared with the younger ones: 49.04% vs 37.22% (p < 0.001) (Table 5.).

Table 6. Number of LN dissected before the introduction of SLN mapping.

	All ages	< 70 y	>70y	p-value
N	247	163	84	
Total # LND (mean)	10.64 ± 5.59	11.34 ± 5.59	9.3 ± 5.36	< 0.05

Table 7. Number of SLN excised after the introduction of SLN mapping.

	All ages	< 70y	>70 y	p-value
N	790	532	258	
Total # LND	7.03±5.99	7.2± 6.19	6.65± 5.56	0.234
Non-sentinel	4.62 ± 5.92	4.71± 6.12	4.42± 5.49	0.502
SLN	2.43± 1.67	2.49± 1.68	2.29± 1.64	0.111

Third objective results:

We evaluated the survival (OS, DFS, CSS) in elderly patients with EC based on the type of surgical procedure (Laparotomy vs Robotic Surgery) and based on the type of lymph node procedure (LND vs SLN). We have included SLN +LND as well as SLN only in the same group. Elderly patients had a significantly better DFS at 3-years (91.8% vs 84.3%, p = 0.03), when comparing SLN mapping vs LND (Fig.11.). No statistically significant difference was observed in OS and CSS in elderly patients, when comparing the type of lymph node procedure (LND vs SLN). The DFS was significantly better in patients undergoing Robotic Surgery vs Laparotomy at 3-years (90.9% vs 81.7%, p = 0.005) (Fig 12.). No statistically significant difference was observed in OS and CSS in elderly patients, when comparing the type of surgical procedure (Robotic vs Laparotomy).

HR for the risk of recurrence in elderly patients undergoing Laparotomy vs Robotic Surgery did not reach statistical significance and neither did the HR for recurrence comparing LND vs SLN.

Figure 11. DFS Kaplan Meier survival curve in elderly patients with EC undergoing LND

vs SLN.

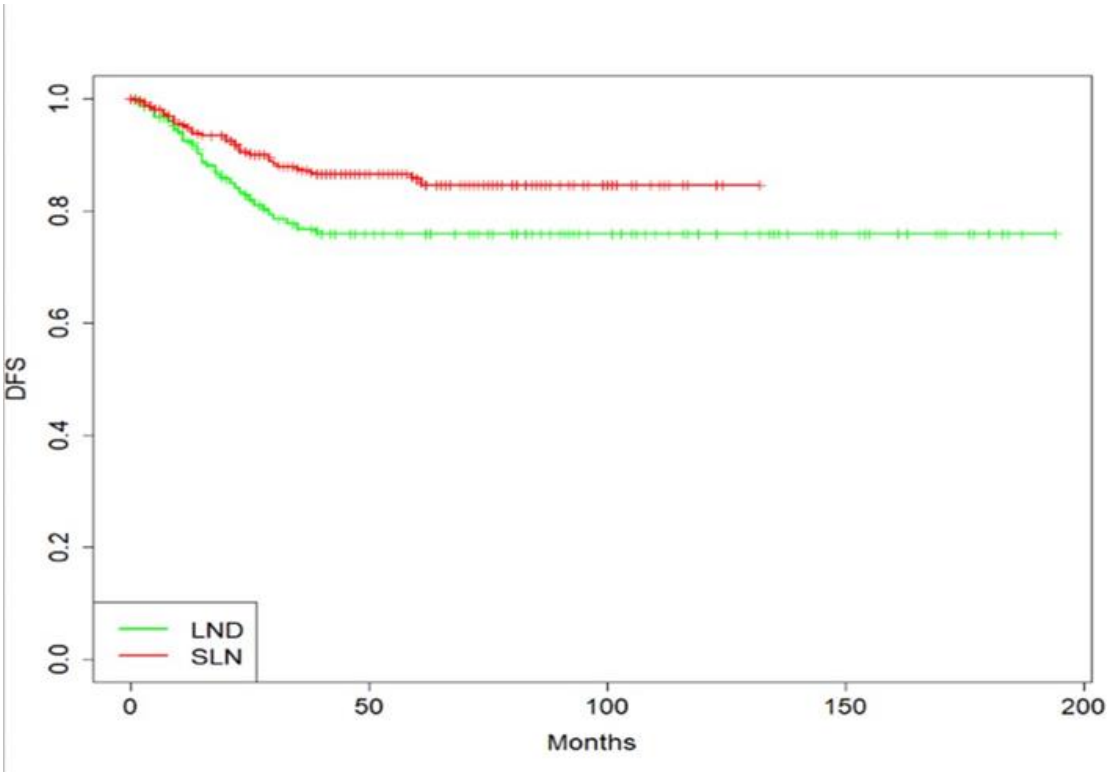
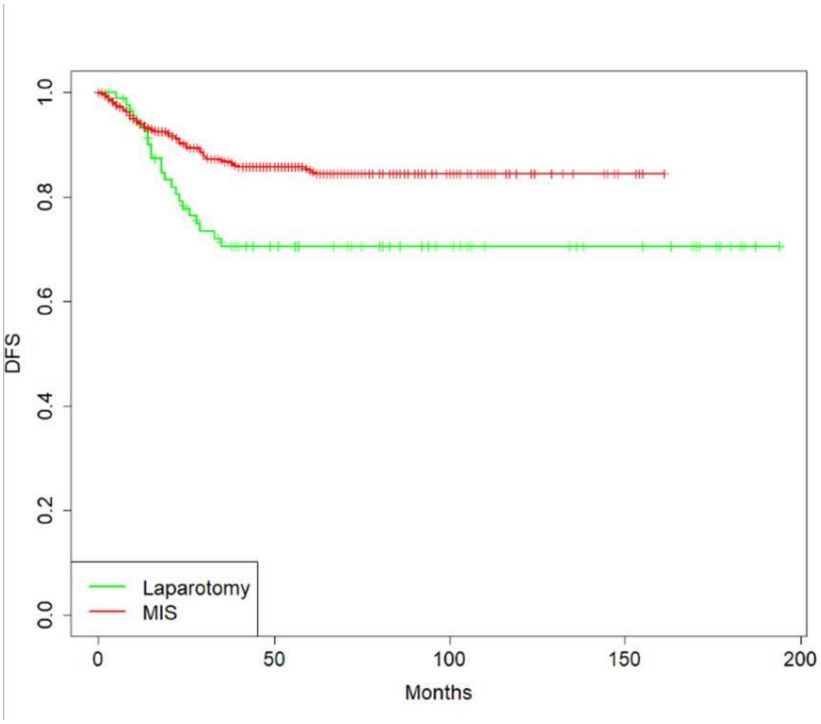


Figure 12. DFS Kaplan Meier survival curve in elderly patients with EC undergoing Robotic Surgery or Laparotomy.



Fourth objective results:

Data from 418 elderly patients with endometrial cancer was evaluated for the presence of frailty markers. The most prevalent frailty marker in this study population was the presence of osteoporosis or osteopenia (16.39%), followed by serum albumin level < 35 g/L (6.88%) and depression (6.18%). 8.35% (35) of these patients had ECOG performance status ≥ 2. One quarter of the patients (25.17%) had at least one of the frailty markers present at the first consultation.

Table 8. Prevalence of evaluated frailty risk factors

Risk factors	N (%)
Albumin < 10	29 (6.88%)
Hemoglobin < 135	20 (4.75%)
BMI < 20	12 (2.85%)
Osteoporosis/osteopenia	59 (16.39%)
Depression	26 (6.18%)
ECOG ≥ 2	35 (8.31%)

Figure 13. Proportion of elderly patients with frailty markers

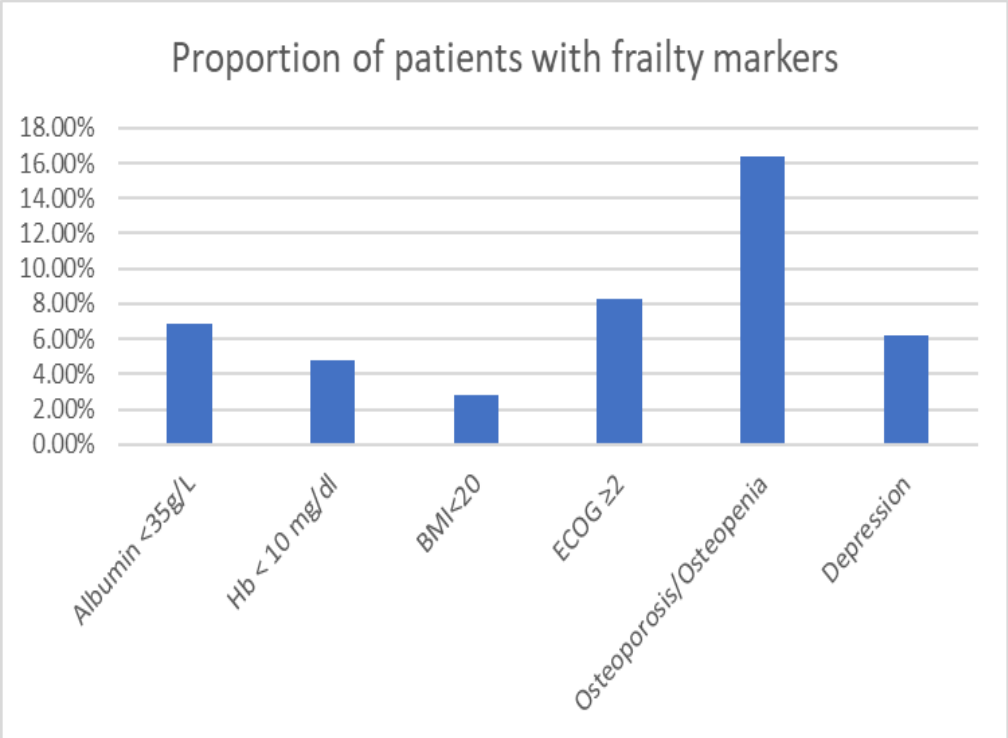


Figure 14. Proportion of elderly patients with one or more frailty markers

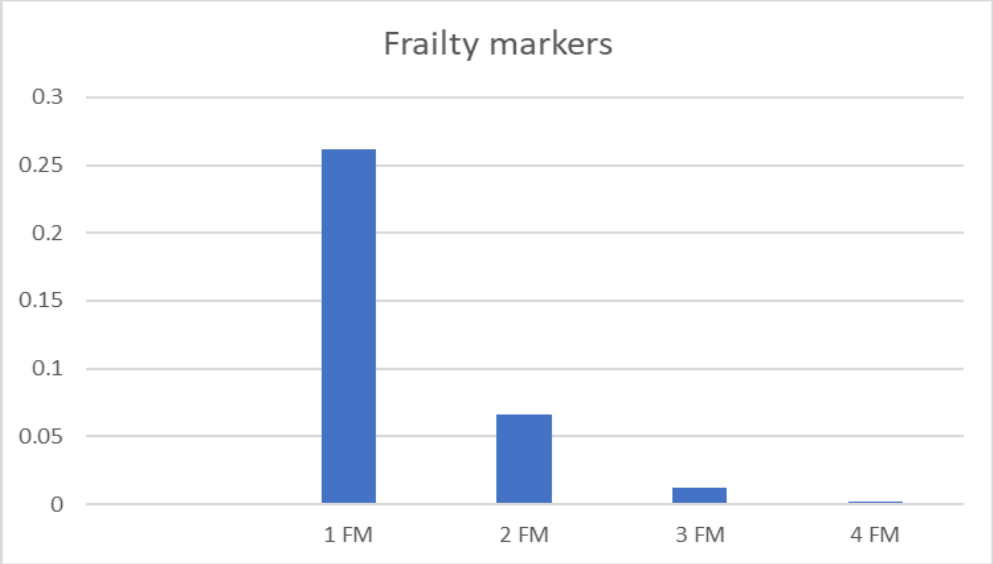


Table 9. Proportion of elderly patients with 1,2,3 or 4 frailty markers

Number of frailty markers	Number of patients (%)
1	106 (25.17%)
2	28 (6.65%)
3	5 (1.19%)
4	1 (0.23%)

We used logistic regression to evaluate the correlation between above mentioned frailty marker and 1-year OS. Hb, BMI, Charlson Comorbidity Index showed correlation with 1-year OS:

The odds of dying decrease by 1.08% every increase of 1 unit of hemoglobin, while all other predictors are held constant.

the odds of dying decrease by 6.71% for every 1 unit increase of BMI, while holding all other predictor variables constant.

66.11% increase odds of death by every 1 unit increase of Charlson Comorbidity Index,

while holding all other predictor variables constant.

Age, albumin levels, depression, osteoporosis/ osteopenia, and ECOG performance status did not reach statistical significance for 1-year OS.

9.3. Discussion

With the increasing incidence of endometrial cancer and a trend of ageing population, the management of elderly patients with cancer occupies a more central role in every day oncologic practice and deserves an objective approach based on data derived from same age cohort.

As we hypothesized, the OS, DFS and CSS is better in younger patients with endometrial cancer than in the elderly ones, but this could be correlated with more advanced stage and more high-grade cancers in the elderly, similar to previously published data [3, 5, 8]. These results correlate with the clinical presentation at the initial visit, where elderly patients presented more often with aggressive histology, higher tumor grade and more advanced FIGO stage of disease, compared with the younger patients.

In contrast to previously published data, with elderly patients receiving less of the adjuvant chemotherapy and radiotherapy compared to the younger patients [10], our data shows elderly receiving more often adjuvant chemo and radiotherapy than the younger patients, in accordance with more aggressive histology, higher tumor grade and more advanced stage of disease at presentation. Patients known to be in palliative care at the last follow-up date were censored in our data analysis. This resulted in a slightly better survival outcome.

For comparison, and to be fully transparent, we calculated the OS, DFS and CSS for entire study population for both scenarios:

Patients known to be in palliative care censored in survival analysis at the last follow-up data: 5-year OS: 89.8%, CI 0.879-0.917; 5-yearDFS: 86.1%, CI 0.839-0.883; 5-year CSS: 91.6%, CI 0.898-0.934.

Patients in palliative care at the last follow-up date coded as deceased: OS: 89.1%, CI 0.872-0.0.911; 5-year DFS: 83.1%, CI 0.808-0.854; 5-year CSS: 90.6%, CI 0.888-0.925.

For the rest of the study, results were obtained using the survival definitions presented in methods, because we considered this to describe existing data more consistent with published literature.

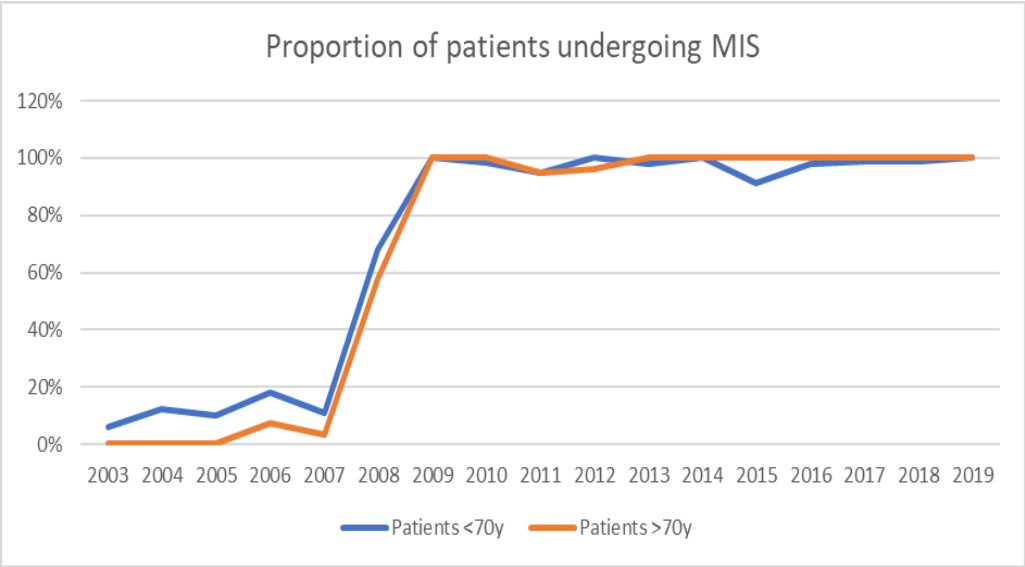
Robotic Surgery was associated with decreased number of peri- and post-operative complications rate, decrease in blood loss and need for transfusions [38], less postoperative pain, and decreased need for analgesic medication as well as faster return to normal activities and shorter hospital stay, without negatively impacting patients' survival [39, 40].

These benefits are particularly important for elderly cancer patients, who often require more aggressive surgical treatment due to the more advanced FIGO stage and tumor histology.

Patients in the younger group received more often Robotic Surgery compared with the elderly patients: 83.96% vs 78.7% ($p<0.02$), while elderly group underwent more often laparotomy compared with the younger age group: 21.05% vs 15.91% ($p < 0.031$). This discrepancy between the two age groups was especially noticeable in the period before the introduction of Robotic Surgery (2003-2008). After this period, the proportions of

patients undergoing Laparotomy or Robotic Surgery become almost identical between the two age groups (Fig.15).

Figure 15. Proportion of patients with EC undergoing Minimal Invasive Surgery



Lymphadenectomy is part of the staging for endometrial cancer patients, providing relevant information regarding the spread of disease beyond uterus and directs the adjuvant treatment.

The number of LN dissected during the staging surgery was significantly lower in the elderly patients (p = 0.005) before the implementation of Sentinel Lymph Node mapping procedure. After this period, the overall number of LN sampled during the staging surgery decreased for both age groups without any statistical significance difference between the two groups.

These results correlate with improved 3-years DFS in elderly patients undergoing SLN vs LND (87.2% vs 76.9%, p = 0.03). Similar, significantly better 3-years DFS was noted in elderly patients undergoing Robotic Surgery vs laparotomy (p = 0.05).

Contrary to previously published data, showing low rates of LND being performed in elderly patients with EC [3,4,5,6], analysis of our data found an improvement in lymph node evaluation since the SLN mapping implementation, with same numbers of SLN dissected during the staging procedure, regardless of the patients' age.

Stratified analysis based on tumor grade and FIGO stage revealed the following:

-stratification based on FIGO stage shows that younger patients with advanced disease (FIGO 3 and 4) have a better survival (OS, DFS and CSS).

-stratification based on tumor grade shows shorter OS and DFS in elderly patients compared with the younger ones, only for tumor grade 1.

Interestingly, no difference in DFS and CSS between the two age groups is noted for tumor grade 2 and 3.

Figure 16. a. OS Kaplan Meier curves for patients FIGO stage 3&4 ($p = 0.02$)

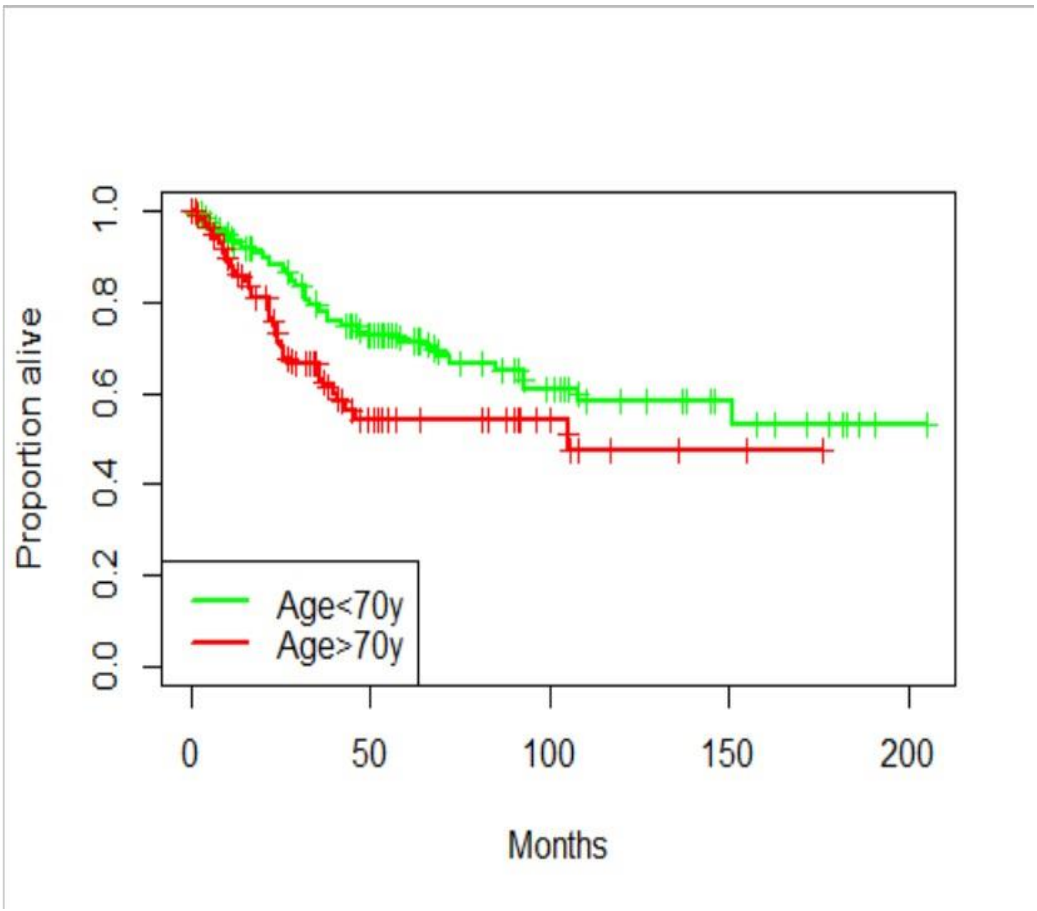


Figure 16. b. DFS Kaplan Meier curves for patients FIGO stage 3&4 (p = 0.02)

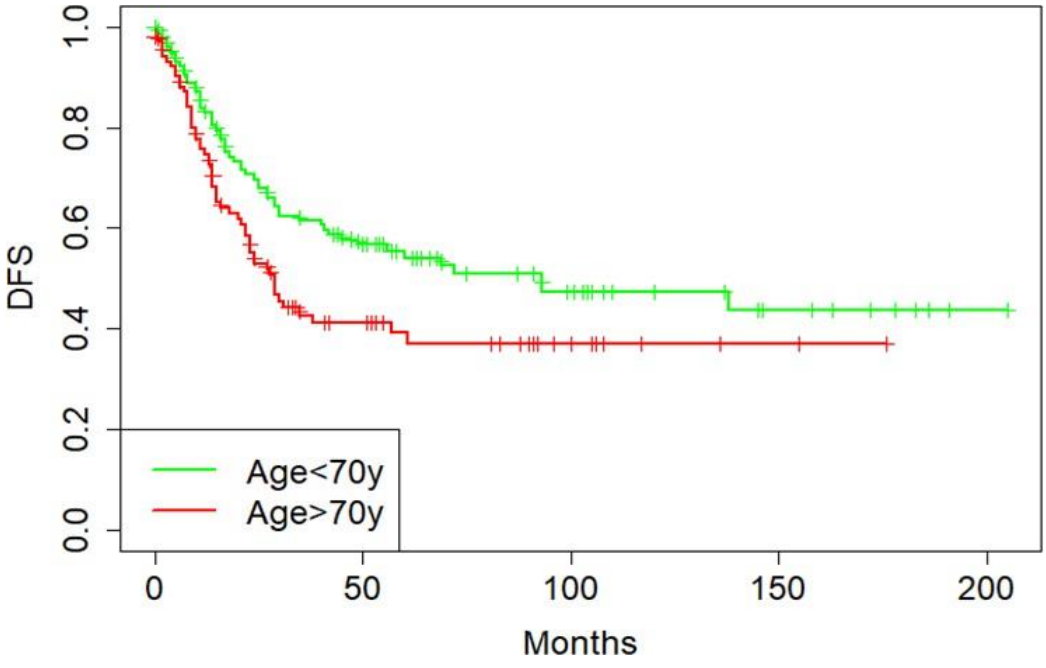
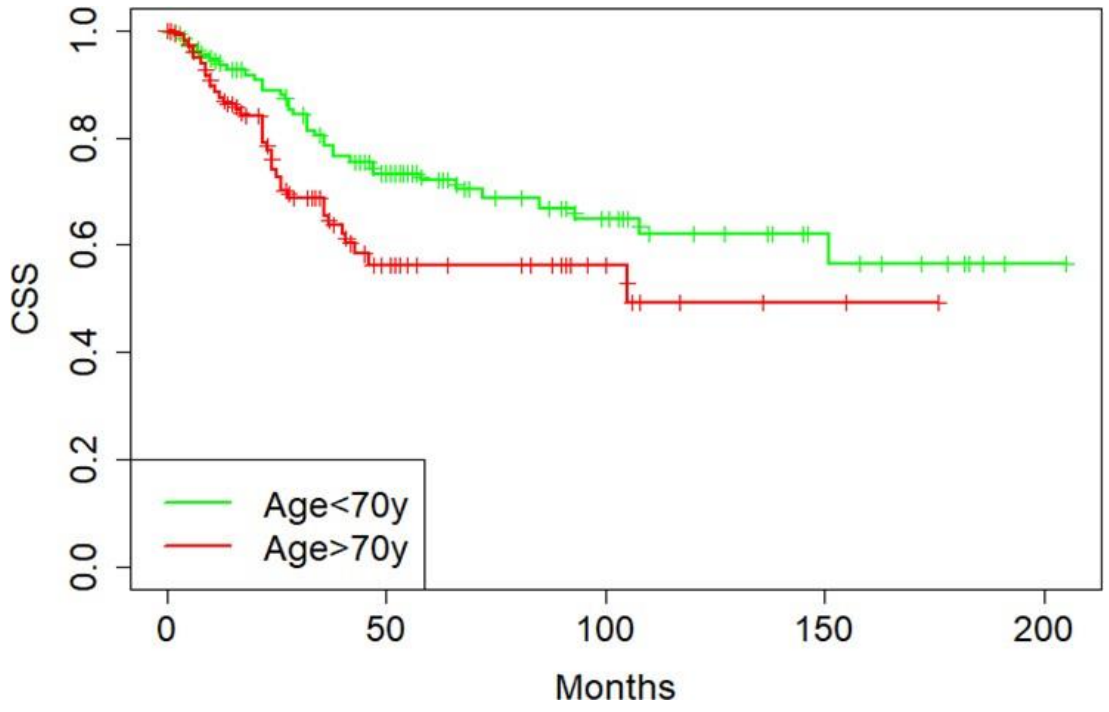


Figure 16. c. CSS Kaplan Meier curves for patients FIGO stage 3&4 (p = 0.03)



Age <70y: 3-years OS: 77.7%, CI 0.703-0.85; 3-years DFS: 61.3%

CI 0.532-0.71; 3-years CSS: 78.4%, CI 0.710-0.865.

Age>70y:3-year OS: 63.1%, CI 0.535-0.744; 3-years DFS: 42.7%, CI 0.336-0.544; 3-years CSS: 65.5%, CI 0.559-0.768.

Kaplan Meier survival curves for the two age groups- stratified by tumor grade (Figure 17. a, b, c, Figure 18. a, b, c, Figure 19. a, b, c).

Figure 17. a. OS Kaplan Meier curves tumor grade1 (p < 0.001)

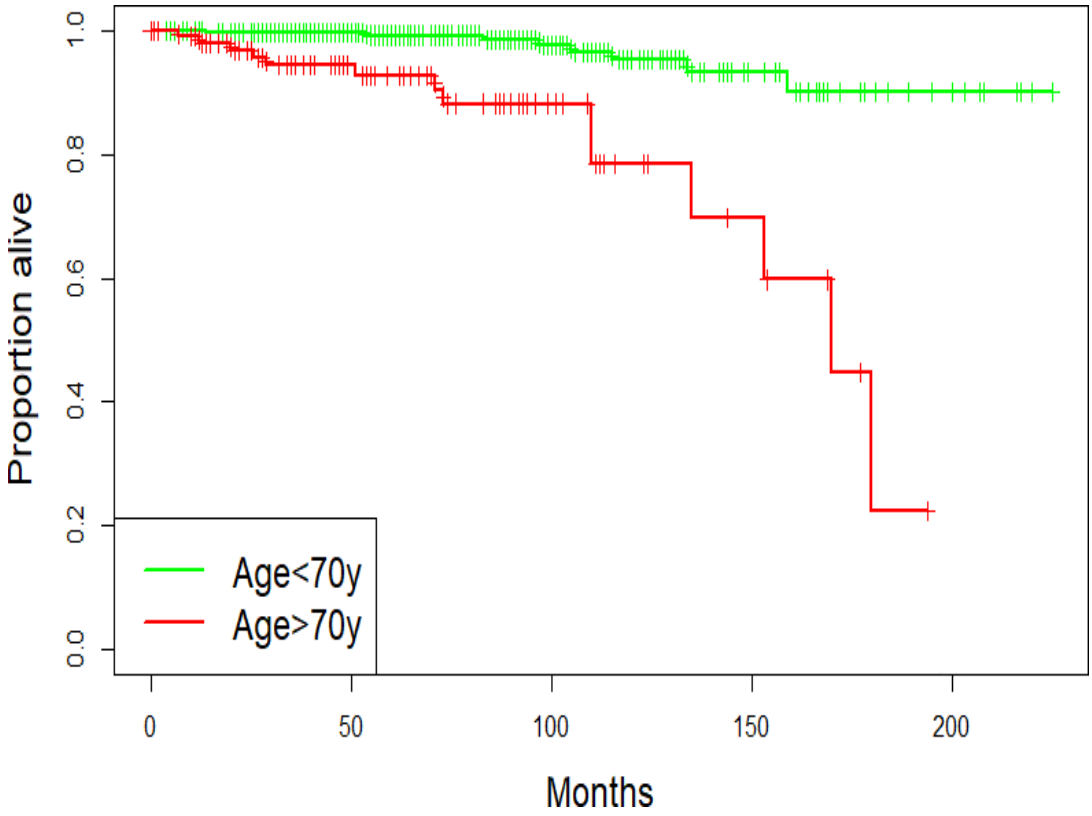


Figure 17. b. DFS Kaplan Meier curves tumor grade 1 ($p < 0.001$)

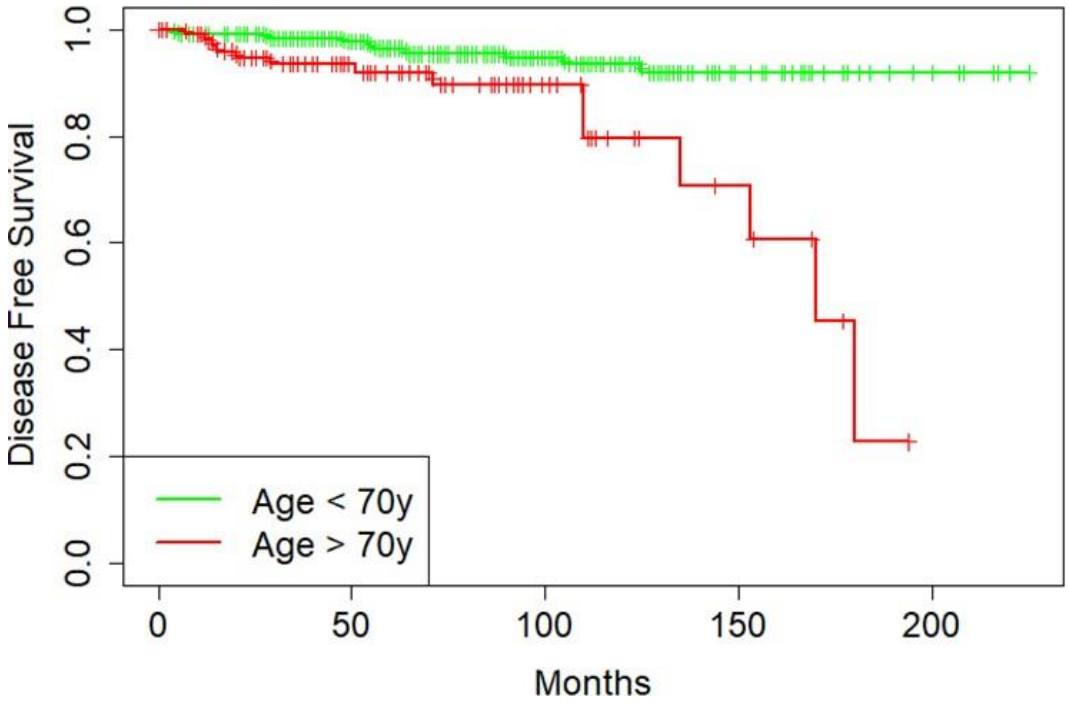


Figure 17. c. CSS Kaplan Meier curves tumor grade 1 (p = 0.9)

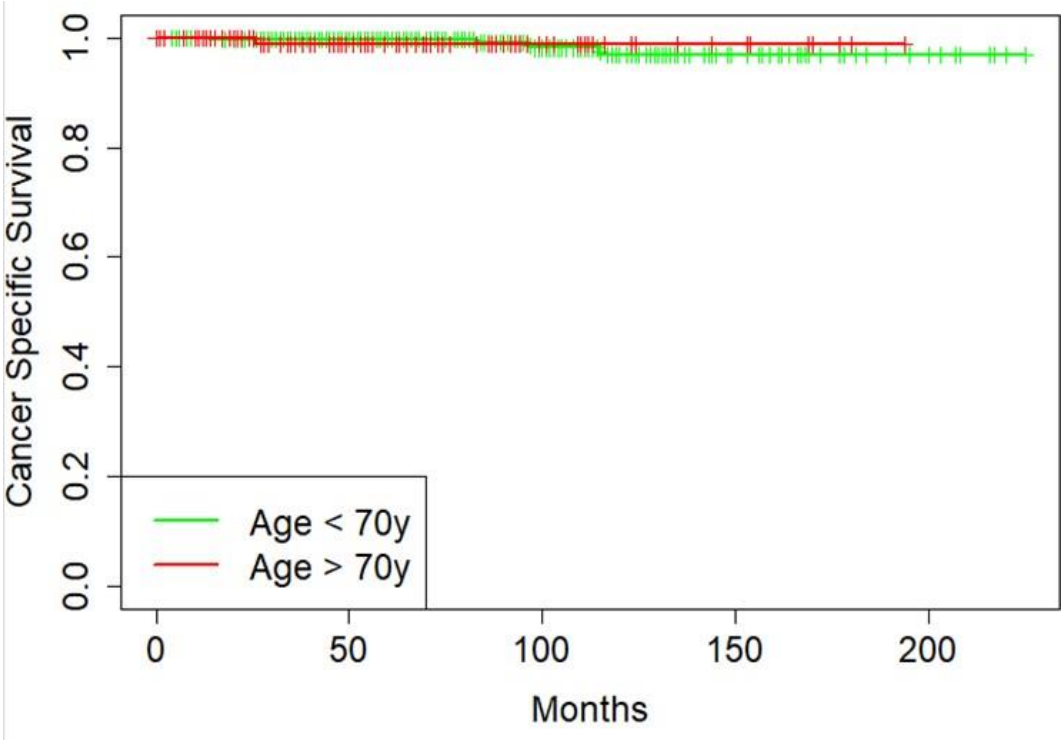


Figure 18. a. OS Kaplan Meier curves tumor grade 2 (p = 0.02)

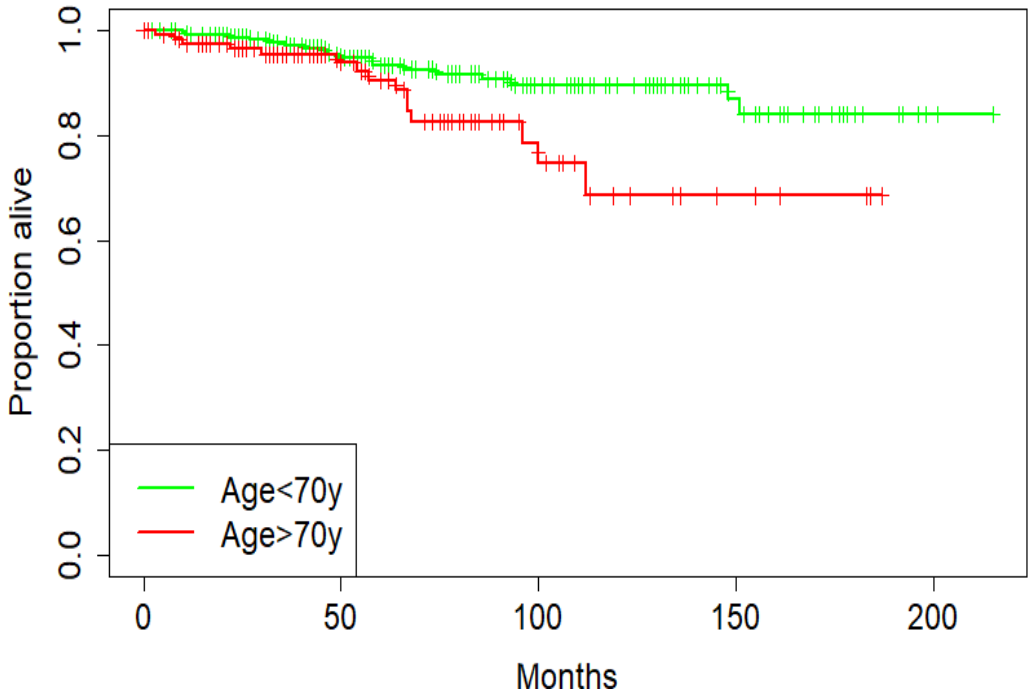


Figure 18. b. DFS Kaplan Meier curves tumor grade 2 (p = 0.08)

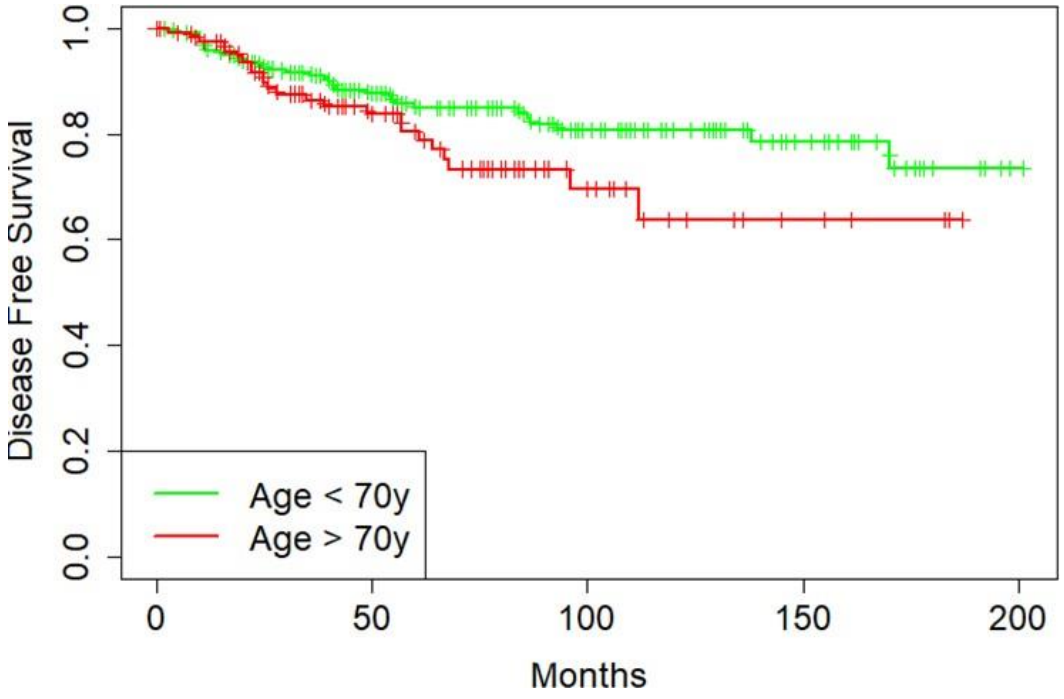


Figure 18. c. CSS Kaplan Meier curves tumor grade 2 (p = 0.9)

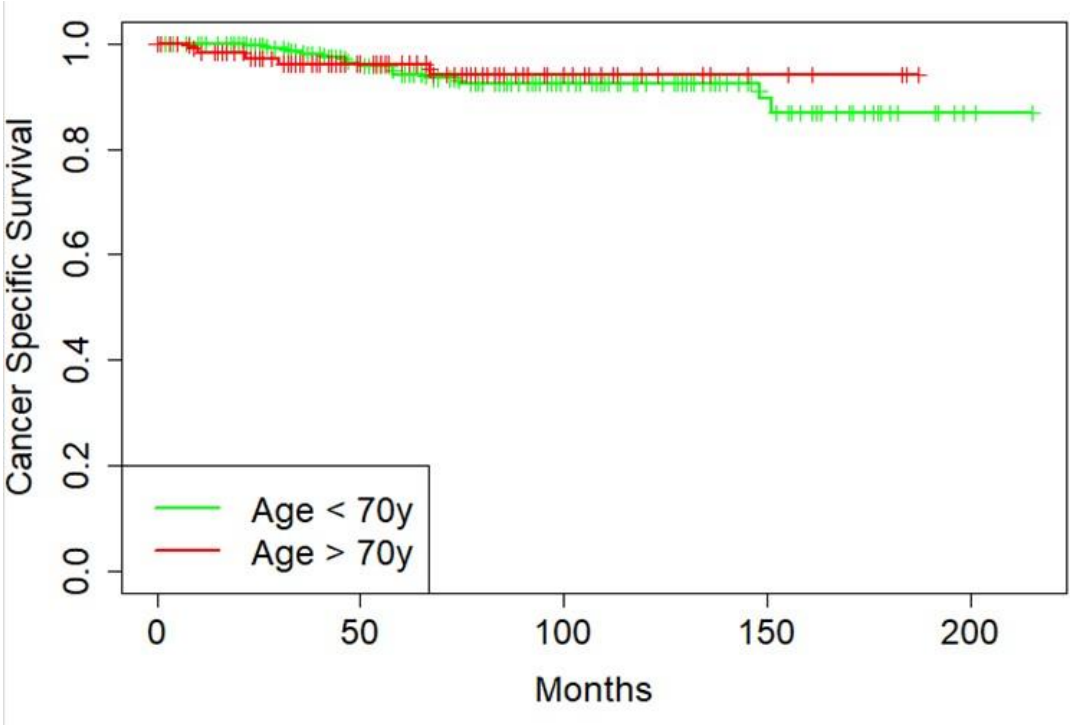


Figure 19. a. OS Kaplan Meier curves tumor grade 3 (p = 0.1)

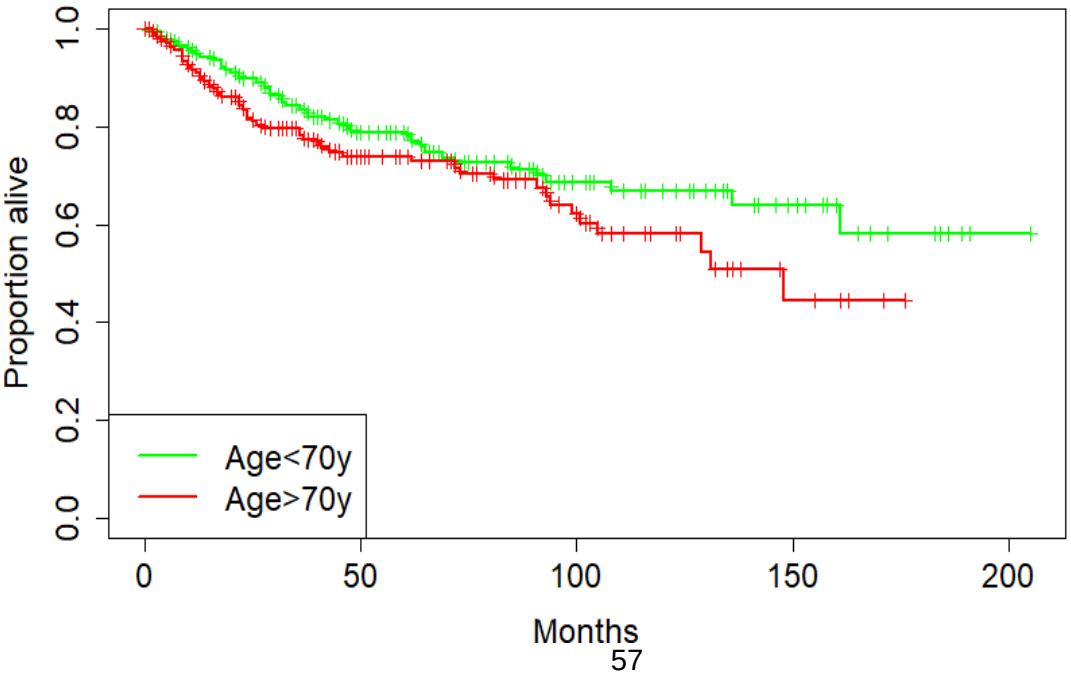


Figure 19. b. DFS Kaplan Meier curves tumor grade 3 (p = 0.09)

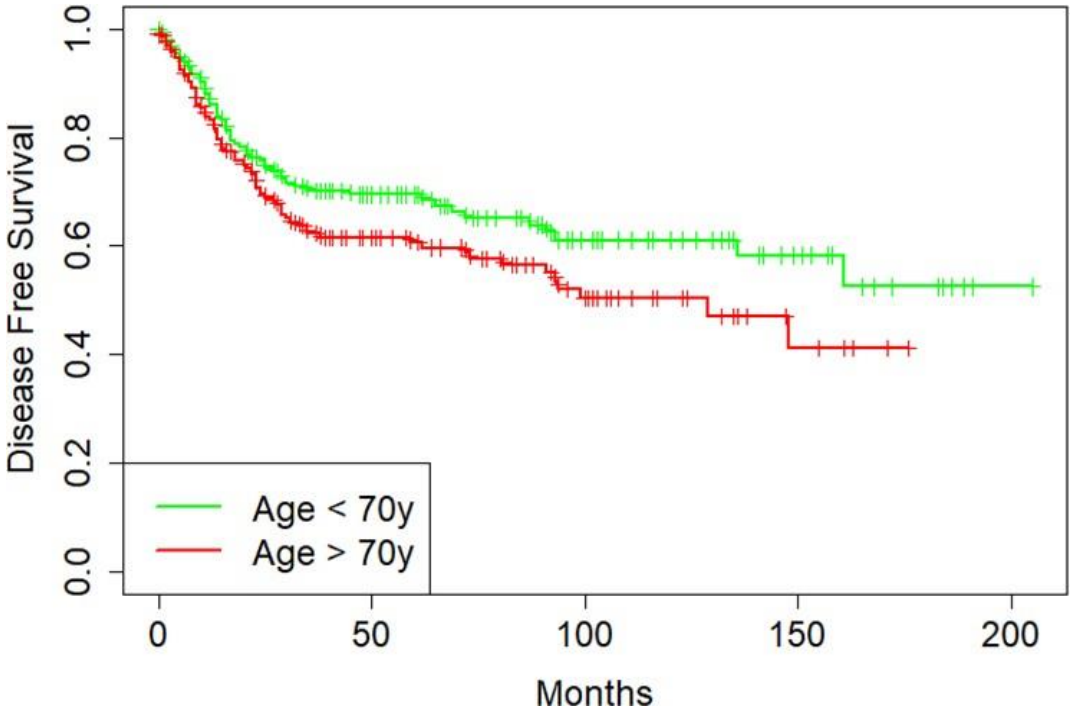
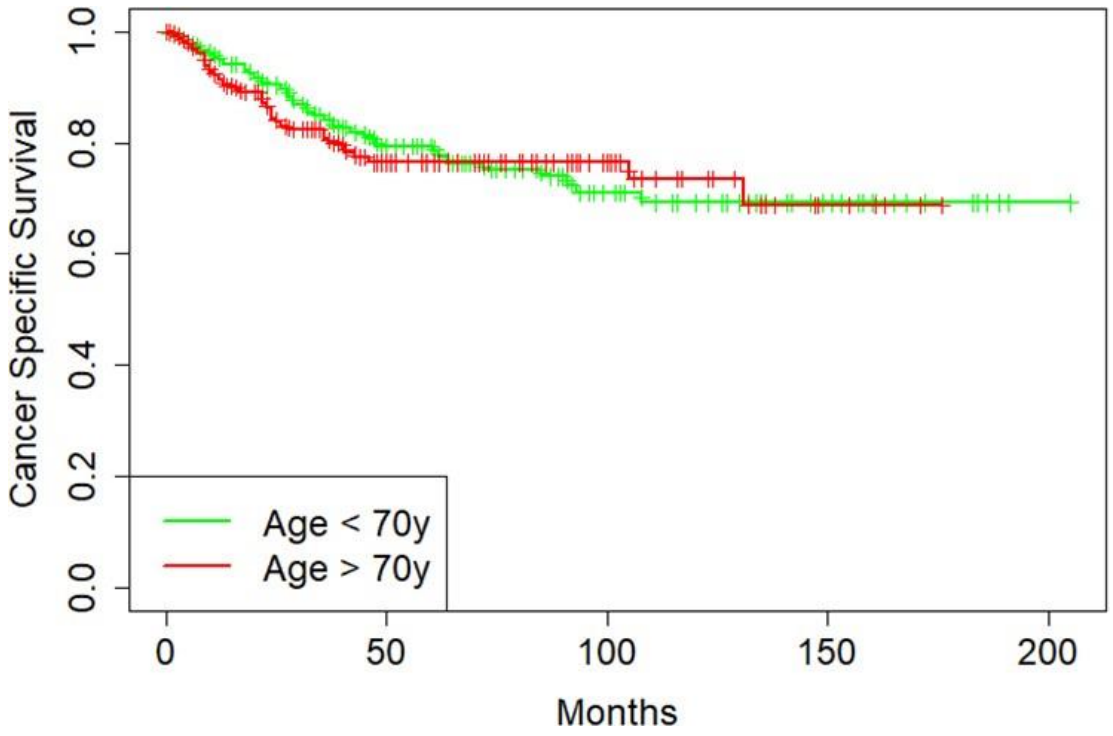


Figure 19. c. CSS Kaplan Meier curves tumor grade 3 (p = 0.8)



Stratified analysis showed that age remains an important variable for the survival of endometrial cancer patients with the same stage of disease. This is not necessarily surprising since advanced age is correlated with several biological factors such as physiological reserve, multiple comorbidities and disease characteristics that ultimately impact survival outcomes.

Stratified analysis based on tumor grade shows DFS curves for the two age groups follow an almost identical trajectory for the first three years, regardless of the tumor grade.

While younger patients with tumor grade 1, with time progression, show a significantly better DFS, for tumor grades 2 and 3, the DFS is similar for both age groups. The very close evolution of the CSS curves for both age groups, over the entire observed period with almost overlapping trajectory, shows that elderly patients can have similar outcomes with the younger ones, for all three tumor grades.

Previous publications used frailty markers (hemoglobin, albumin, osteoporosis/osteopenia, depression and ECOG) in different cancer populations.
We have analyzed data from our patient population to identify the prevalence of these frailty markers and evaluate the correlation with 1-year OS.
One quarter of the elderly patients with EC had at least one of the frailty markers, while only 8.7% had two or more.
Our data analysis showed that hemoglobin level, BMI and Charlson Comorbidity Index correlated with 1-year OS in elderly patients. No correlation was found between age, presence of osteoporosis or osteopenia, albumin level, ECOG performance status or depression with 1-year OS. We decided to evaluated the correlation between the above frailty markers and 1-year OS rather than 3-years OS because over an extended period of time, other factors such, as advanced age, may influence the OS.
Study limitations are related to the retrospective nature of this cohort study: although rare, some missing data and risk factors for recurrence like molecular analysis and LVSI were not systematically recorded in older data. Another limitation is the fact that the results are based on data obtained from a single center, in one city and it is not generalizable for other centers or geographic areas. In order to generalize these results, we would need data from multiple centers.

9.4. Conclusions:

In this study, OS, DFS and CSS in younger women with endometrial cancer was statistically better that in the elderly women, which can be correlated with more advanced stage of disease more high-grade tumors in the elder patients. In our elderly

patients, only hemoglobin, BMI, and Charlson Comorbidity Index were associated with 1-year OS. Considering the prognostic value of these frailty markers on survival, they can contribute to the development of personalized treatment plans and optimizations of supportive care.

Despite advanced age and more comorbidities, elderly women with endometrial cancer can not only safely undergo robotic surgery for staging, similarly with younger women (<70 years), but the3-years DFS was significantly better in elderly patients undergoing robotic surgery vs laparotomy.

Similarly, 3-year DFS was significantly better in elderly patients undergoing sentinel node dissection versus complete lymphadenectomy. In addition, when we performed a stratified analysis based on tumor grade the cancer specific survival was similar for both age groups. This suggests that when taking in consideration tumor grade, advanced patient age is not a major determinant of cancer specific survival.

Evaluating the trends of treatment in endometrial cancer patients under and over the age of 70, our analysis suggests that minimally invasive surgery, specifically robotic surgery, and SLN dissection appear to be safe in elderly patients. However, before establishing this treatment approach as standard, it may be prudent to correlate our findings with data from elderly patients at other medical centers.

10. Reference list

1. Cancer Statistics Center. American Cancer Society. https://cancerstatisticscenter.cancer.org/#!/data- analysis/Incidence Trend.

2. Gaber C., Meza R., Ruterbusch J.J., Cote M.L. Endometrial cancer trends by race

and histology in the USA: projecting the number of new cases from 2015 to 2040. J Racial Ethn Health Disparities. Published online October 17, 2016.

3. Poupon C., Bendifallah S., Ouldamer L., Canlorbe G., Raimond E., Hudry N., Coutant C., Graesslin O., Touboul C., Collinet P., Bricou A., Huchon C., Darai E., Ballester M., Leveque J., Lavoue V., Management and Survival of Elderly and Very Elderly Patients with Endometrial Cancer: An Age- Stratified Study of 1228 Women from the FRANCOGYN. Ann Surg Oncol 2017; 24:1667–1676Group.

4. Koual M., Ngo C., Girault A., Bats S.A., Endometrial cancer in the elderly: does age influence surgical treatments, outcomes, and prognosis? Menopause: The Journal of The North American Menopause Society Sept 2018; 25, (9): 968- 976.

5. Benito V., Lubrano A., Andujar M., Mori M., Federico M., Management of endometrial cancer in patients aged 80 years and older Identifying patients who may benefit from a curative treatment. European Journal of Obstetrics & Gynecology and Reproductive Biology 2019 Nov; 242: 36– 42.

6. Guy M.S., Sheeder J., Behbakht K., Wright J., Guntupalli S.R., Comparative outcomes in older and younger women undergoing laparotomy or robotic surgical staging for endometrial cancer American Journal of Obstetrics & Gynecology 2016 Mar; 214(3): 350.e1-350.e10.

7. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer Clin. 2018; 68(6): 394-424.

8. Canadian Cancer Society. CCS website. https://cancer.ca/en/cancer-information/cancer-types/uterine.

9. Bourgin C., Lambaudie E., Houvenaeghel G., Foucher F., Leveque J., Lavoue V. Impact of age on surgical staging and approaches (laparotomy, laparoscopy, and robotic surgery) in endometrial cancer management; EJSO 43 (2017) 703e709.
10. Rauh-Hain J.A., Pepin K.J., Meyer L.A., Clemmer J.T., Lu K.H., Rice L.W., Uppal S., Schorge J.O., Del Carmen M.G., Management for elderly women with advanced-stage, high-grade endometrial cancer. Obstetrics& Gynecology 2015, 126(6):1198-1206
11. Eggemann H., Ignatov T., Burge E., Costa S.D., Ignatov A., Management of elderly women with endometrial cancer. Gynecologic Oncology 2017; 146 (3) 519–524
12. Lavoué V., and Gotlieb W., Benefits of minimal access surgery in elderly patients with pelvic cancer. Cancers (Basel). 2016; 8 (1):12.
13. Backes F.J, ElNaggar A.C., Farrell M.R., Brudie L.A., Ahmad S., Salani R., Cohn D.E., Holloway R.W., Fowler J.M., O'Malley D.M., Perioperative outcomes for laparotomy compared to robotic surgical staging of endometrial cancer in the elderly. A retrospective cohort. International Journal of Gynecological Cancer, 2016 Nov; 26(9):1717-1721.
14. Zacharia A., Czuzoj-Shulman N., Spence A.R., Gotlieb W.H., Abenhaim H.A., Hysterectomy for Uterine Cancer in the Elderly: A Comparison Between Laparoscopic and Robot-Assisted Techniques. Int J Gynecol Cancer. 2016 Sep; 26(7):1222-7.
15. Zhou L., Gou F., Li D., Qi J., Chan L., Yuan Y., Short- and long-term outcomes of laparoscopic surgery for elderly patients with clinical stage I endometrial cancer; J BUON. 2020; 25(2): 764-771.
16. Gallotta V, Conte C., D'Indinosante M., Federico A., Biscione A., Vizzielli G., Bottoni C., Carbone M.V., Legge F., Uccella S., Ciocchetti P., Russo A., Polidori L., Scambia

G., Ferrandina G., Robotic surgery in elderly and very elderly gynecologic cancer patients. J Minim Invasive Gynecol Jul- Aug 2018;25(5):872-877.

17. Torgeson A., Boothe D., Poppe M.M., Suneja G., Gaffney D.K., Disparities in care for elderly women with endometrial cancer adversely affect survival. Gynecologic Oncology 2017 Nov; 147 (2) 320–328.

18. Meyers B., Ndong S., Guy J.B., Assouline A., Falk A.T., Valeille A., Trone J.C., Rivoirard R., Auberdiac P., Vallard A., Espenel S., Moriceau G., Collard O., Bosacki C., Jacquin J.P., De Laroche G., Fournel P., Chargari C., Magne N., Radiotherapy for gynecologic cancer in nonagenarian patients: a framework for new paradigms. Méry et al. Chin J Cancer 2016 May; 35:43.

19. Nikolopoulos M., Godfrey M., Wuntakal R., Medically unfit women with early-stage endometrial cancer treated with the levonorgestrel intrauterine system. Obstet Gynecol Sci 2020;63(3):337-345.

20. Gardella B., Dominoni M., Bogliolo S., Cassani C., Carletti G.V., De Silvestri A., Spinillo A., Palliative treatment of endometrial cancer: what is the role of anastrozole in elderly women? Gardella et al. BMC Palliative Care 2021 Feb; 20(1): 28.

21. Bellera C.A., Rainfray M., Mathoulin-Pelissier S., Mertens C., Delva F., Fonck M., Soubeyran P.L., Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Incol. 2012 Aug; 23(8):2166-2172.

22. Klapheke A.K., Keegan T.H.M., Ruskin R., Cress R.D., Pre-diagnosis health-related quality of life and survival in older women with endometrial cancer. Supportive Care in Cancer. 2020 Oct; 28(10):4901–4909.

23. Mohile S.G., Dale W., Somerfield M.A., Boud C.M., Burhenn P.S., Canin B., Cohen

H.J., Holmes H.M., Hopkins J.O., Janelsins M.C., Khorana A.A., Klepin H.D., Lichtman S.M., Mustian K.M., Tew W.P., Huria A., Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J of Clinical Oncology. 2018 Aug; 36(22): 2326-2347.

24. Yoshida H., Shintani D., Kawashima N., Fujiwara K., Predicting toxicity of platinum and taxane-based chemotherapy in older patients with gynecologic cancer. JBUON 2020; 25(2): 736-742.

25. Huria A., Mohile S., Gajra A., Klepin H., Muss H., Chapman A., Feng T., Smith D., Sun C.L., De Glas N., Cohen H.J., Katheria V., Doan C., Zavala L., Levi A., Akiba C., Tew W.P., Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. Journal of clinical oncology. 2016 Jul; 34(20):236-71.

26. Michaan N., Park S.Y., Lim M.C., Comprehensive geriatric assessment is correlated to overall survival among gynecologic oncology patients. Japanese Journal of Clinical Oncology, 2020. 50(3):276-281.

27. Nadaraja S.,Matzen L.E., Jorgensen T.L., Dysager L., Knudsen A.O., Jeppesen S.S., Moller S., Herstedt J., The impact of comprehensive geriatric assessment for optima treatment of older patients with cancer: A randomized parallel-group clinical trial. Journal of Geriatric Oncology. 2020 Apr; 11(3):488-495.

28. Hamaker M.E., Molder M.T., Thielen N., Van Munster B.C., Schiphorst A.H., Van Huis L.H., The effect of geriatric evaluation on treatment decision and outcome for older cancer patients - a systematic review. J Geriatric Oncol. 2018 Sep; 9(5):430-40.

29. Richards S.J., Frizelle F.A., Geddes J.A., Eglinton T.W., Hampton M.B., Frailty in surgical patients. Int J Colorectal Dis. 2018 Dec; 33(12):1657-1666.

30. Adedayo P., Resnick K., Singh S., Preoperative frailty is a risk factor for non-home discharge in patients undergoing surgery for endometrial cancer. Journal of Geriatric Oncology 2018 Sep; 9(5): 513–515

31. Sia T.Y., Wen T., Cham S., Friedman A.M., Wright J.D., The effect of frailty on postoperative readmissions, morbidity, and mortality in endometrial cancer surgery. Gynecologic Oncology 2021 May; 161(2): 353–360.

32. Driver J.A., Viswanathan A.N., Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older. Gynecol Oncol. 2017 June; 145(3): 526–530.

33. Inchi M.G., Anders L., Heise K., Richter R., Woopen H., Sehouli J, Can Fried Frailty Score predict postoperative morbidity and mortality in gynecologic cancer surgery? Results of a prospective study. Journal of Geriatric Oncology 2020 Apr; 12(3):428-433.

34. Ferrero A., Villa M., tripodi E., Fuso L., Menato G., Can Vulnerable Elderly Survey-13 predict the impact of frailty on chemotherapy in elderly patients with gynecological malignancy? Medicine (Baltimore)2018Sep; 97(39):e12298.

35. Orlandini L., Nestola T., Colloca G.F., Ferrini A., Cesari M., The Frailty Index in older women with gynecologic cancer. Aging Clinical and Experimental Research 2020Aug; 32(8):1561–1565.

36. Yamamoto M., Yoshida Y., Itani Y., Sato S., Futagami M., Sakai H., Kajiyama H., Aoki Y., How doctors choose treatment for older gynecological cancer patients? A Japanese Gynecology Oncology Group survey of gynecologic oncologists. International Journal of Clinical Oncology 2020Apr; 25(4):741–745.

37. National Comprehensive Cancer Network Guidelines V 1. 2024. Endometrial

Carcinoma. Principles of evaluation and surgical staging when SLN mapping is used. https://www.nccn.org/guidelines

38. Uccella S., Franchi M.P., Cianci S., Zorzato P.C., Bertoli F., Alletti S.G., Ghezzi F., Scambia G., Laparotomy vs minimally invasive surgery for ovarian cancer recurrence: a systematic review. Gland Surg. 2020Aug; 9(4): 1130-1139.

39. Jung J., Noh J.J., Choi C.H., Kim T.J., Lee W.J., Kim T.G., LeeY.Y., Minimally invasive versus abdominal hysterectomy for endometrial cancer with glandular or stromal invasion of cervix. Front Oncol. 2021 May; 11:670214.

40. Sofer A., Magnezi R., Eitan R., Raban O., Tal O., Smorgic N., Vaknin Z., Robotic vs open surgery in obese women with low-grade endometrial cancer: comparison of costs and quality of life measures. Isr. J. Health Policy Res. 2020 Nov; 9(1):60.

11. Appendices:

11.1 Appendices 1. Authorization to conduct research by Institution Review Ethics Board

2021-11-12

Dr. Walter Gotlieb Gynecology-oncology c/o: Florentine Racovitan Gynecology-oncology

email: fracovitan@gmail.com

Object: Project 2022-3038 - Final Authorization to conduct research at the CIUSSS West-Central Montreal

Overview of the management of elderly patients with Endometrial Cancer

Comply with the Regulatory Framework of our Institution with regards to research activities, including the requirements for the respect and privacy of research

participants.

Use the version of the research documents approved by the CIUSSS WCM REB, the only changes made, if any, being administrative and identified so that the CIUSSS WCM REB can read them.

Respect the mechanisms required for annual review determined by the CIUSSS WCM REB.

Respect the procedures of the MSSS Multicenter Mechanism with regards to respect and privacy of research participants specifically, the identification of the research participants at our Institution, that is maintaining and keeping up to date the list of the participants recruited into the study at our Institution. This list must be submitted to us upon request.

Preserve the research files during the prescribed period of any applicable regulations or by the CIUSSS WCM REB, after the end of the project, in case of an audit, and to notify the reviewing REB and Person Formally Mandated the ongoing conduct of the project, with regards to new modification to the research.

*COVID-19

The COVID-19 pandemic and the state of emergency declared by the Province of Quebec create exceptional circumstances, having impacts on research activities, in particular their evaluation and conduct. In this context, the conduct of this study must be aligned with the specific guidelines in effect at the CIUSSS du Center-Ouest-de-l'Île- de-Montréal and in each respective participating institution, if applicable.

This authorization hereby grants you to perform research under the auspices of our Institution and must be prior to the date specified by the CIUSSS WCM REB decision to

renew its research ethics approval of this research. It will be renewed without further procedure on the date indicated by the CIUSSS WCM REB in his decision to renew his approval ethics of this research.

Respectfully,

Geneviève Lamy

Directrice adjointe | Associate Director

Directrice adjointe des affaires académiques et de l'éthique de la recherche | Directorate of Academic Affaires and Research Ethics

CIUSSS du Centre-Ouest-de-l'Île-de-Montréal | CIUSSS West-Central Montreal

Pour/For Cindy Starnino

Directrice des Affaires académiques | Director of Academic Affairs

Personne mandatée par l'établissement pour autoriser la réalisation des projets de recherche CIUSSS du Centre- Ouest-de-l'Île-de-Montréal | CIUSSS West-Central Montreal

11.2. Appendices 2. Copyright

Copyright Figure 1. Bar Chart of Incidence and Mortality Age Standardized Rates, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Order summary: Licensee McGIl University; Order Number: 5063181351153.

Copyright Figure 2. Overall Survival for Woman with Endometrial Cancer A) and B). Eggemann H., Ignatov T., Burge E., Costa S.D., Ignatov A., Management of elderly women with endometrial cancer. Gynecologic Oncology 2017; 146 (3) 519–524 ISSN: 0090-8258