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ENDOMETRIAL CANCER OF THE VERY ELDERLY: MANAGEMENT AND SURVIVAL IN THE FRANCOGYN POPULATION**CRedit author statement**

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ENDOMETRIAL CANCER OF THE VERY ELDERLY: MANAGEMENT AND SURVIVAL IN THE FRANCOGYN POPULATION

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Abstract

Introduction. We aimed to describe management and survival of patients with endometrial cancer (EC) ≥ 80 years to identify poor prognosis criteria.

Methods. We collected clinical, histologic, surgical and follow-up data for patients with EC ≥ 80 years included in a multicenter French cohort (FRANCOGYN) who underwent primary surgical treatment from 1999 to 2019. The outcomes were overall survival (OS) and disease-free survival (DFS). We performed a descriptive analysis then a survival time analysis and comparison using the Kaplan Meier method and log-rank test.

Results. Of the 1647 patients with EC who received treatment during the study period, 184 (11.17%) were ≥ 80 years. The mean age was 84 years (± 3.34). Thirty-three patients (25.4%) died during the follow-up period and 26 relapsed (18.4%). Forty-nine patients were lost to follow-up (27.37%). The median follow-up time was 15.3 months (4.9-28.8). The median OS and DFS was 16.4 months (6.3-24.9) and 13.6 months (4.5-26.6), respectively. Eighty-three patients received adjuvant therapy (45.11%), out of 95 who had a formal or relative indication. Four patients received adjuvant chemotherapy (2.6%), out of 61 who had a formal or relative indication. Inappropriate or underuse of chemotherapy was significantly associated with a lower median OS of 12.6 months [3.73-24] versus 17.3 months [7.93-41.77] when performed appropriately (HR=4.14, CI 95% [1.62-10.56]), and a lower median DFS of 10.83 months [3.73-24] versus 17.3 months [7.93-28.5] (HR=9.04, CI 95% [2.04-40.12]).

Conclusion. Our results suggest that very elderly patients with EC should receive adjuvant chemotherapy according to the standard care guidelines.

Key-words : surgical oncology – endometrial cancer – elderly – adjuvant treatment - survival

Introduction

Endometrial cancer (EC) is the most common pelvic gynecologic malignancy in Europe (1), with 8224 new cases per year in France in 2018 (2). It is the fifth deadliest cancer in women (3) with a 76% five-year survival chance in Europe in 2000-2007 (4). Age is a main risk factor for this disease (3) which explains the increase in incidence observed over the last decades as the population is aging in developed countries (5). This progression is expected to continue during the coming years, making EC a major public health concern.

Endometrial cancer in older patients gives rise to several challenges. These patients seem to be at a higher risk of aggressive histologic types (6), and are more likely to present with an advanced stage due to late diagnosis (7). Geriatric oncologic care has its own specific issues in terms of global patient evaluation and treatment strategies, taking comorbidities into account, as well as specific nutritional, social, and psychiatric needs. This might lead to disparities in access to appropriate treatment in elderly patients with EC. For example, surgical staging is not always performed when indicated in patients of 80 years or older (8, 9), and this has been shown to negatively influence survival in a British cohort (10). Similarly, previous studies have reported that elderly patients receive less aggressive treatment than their younger counterparts for a similar histologic stage (11), especially concerning adjuvant treatment such as radiotherapy (8, 10, 12) or chemotherapy when indicated. Moreover, these treatments are not significantly associated with an increase in cancer-specific complications when performed (13), and there is a known benefit for patients with high-risk tumors which are overrepresented in elderly populations (14).

Overall, despite the increase in the proportion of very elderly patients with EC, there are still no specific guidelines on diagnosis and treatment strategies. The few studies involving this population suggest that they lack access to staging and treatment options compared to standard care guidelines, resulting in a poorer outcome (6, 15).

Therefore, the objective of this study was to describe treatment management and survival in patients with EC aged 80 years and older in a large French cohort to identify risk factors of poor prognosis.

Methods

- Study population

We retrospectively analyzed data collected from a database of patients with EC who received primary surgical treatment between 1999 and 2019. The data were obtained from 10 institutions in France who maintain EC databases (Tours, Tenon, Dijon, Rennes, Lille, Reims, Creteil, Poissy, Bondy, and Clermont Ferrand Tertiary Hospitals) and from the SENTI-ENDO trial (16). Each of these institutions have high gynecologic oncologic caseloads and perform more than 70 gynecologic oncologic surgical procedures per year. The research protocol was approved by the Institutional Review Board of the National College of French Obstetricians and Gynecologists (CNGOF) in 2014 (CEROG 2014-GYN-020). For this study, patients 80 years of age and older were selected.

- Collected data

All the patients had undergone a preoperative endometrial biopsy and abdominopelvic magnetic resonance imaging unless contraindicated, in which case a computed tomography scan was performed.

The demographic and clinical data collected included: age, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), and comorbidities (hypertension, diabetes, menopausal hormone therapy, history of breast cancer). Surgical data (surgical approach, nodal staging), histologic data (subtype, grade and stage based on the International Federation of Gynaecology and Obstetrics (FIGO 2009)) (17), risk group based on the European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) classification (18), and adjuvant therapy were also collected.

Lymph nodes were considered positive when macro- or micrometastases were present. A tumor was considered to have lympho-vascular space invasion (LVSI) when tumor emboli were found within a space clearly lined by endothelial cells on a hematoxylin and eosin-stained section.

The women underwent primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy, with or without nodal staging (pelvic and paraaortic lymphadenectomy) according to the guidelines in place at the time of diagnosis and at the surgeon's discretion. The European guidelines recommend pelvic and paraaortic lymph node surgical staging for high-risk groups. Adjuvant therapy included vaginal brachytherapy (VBT), and/or external beam radiotherapy (EBRT), and/or chemotherapy (CT), and clinical follow-up. Adjuvant therapy was administered on an individual basis at the discretion of a multidisciplinary committee based on the European guidelines (18). Missing data about the ESMO/ESGO/ESTRO risk groups was imputed as follows when the information was available: low risk (stage 1A grade 1 or 2 histologic type 1 tumors LVSI negative or focal), intermediate risk (stage 1A grade 3 histologic type 1 tumors LVSI negative or focal, or stage 1B grade 1 or 2 histologic type 1 tumors LVSI negative or focal, and stage 1A histologic type 2 tumors without myometrial invasion), high-intermediate risk (HIR) (stage 1 endometrioid type 1 tumors with substantial and not focal positive LVSI, or stage 1B grade 3 tumors, and stage 2 tumors), high risk (stage 3 and 4a tumors without residual disease, and type 2 tumors with myometrial invasion), and advanced (stage 4b tumors, or stage 3 and 4a tumors with residual disease) (18).

Clinical follow-up consisted of physical examinations and the use of imaging techniques according to the findings.

The main outcome measures were overall survival (OS) (calculated from the date of surgery to death, whether related or unrelated to cancer) or date of last follow-up for surviving patients, and disease-free survival (DFS) (calculated as time from the date of surgery to cancer recurrence). Biopsy or imaging studies were used to diagnose recurrence which was defined as local or distant relapse.

- Statistical analyses

Descriptive quantitative continuous variables are expressed as the mean (\pm Standard Deviation [SD]) and median [range] when indicated. Descriptive qualitative variables are presented as frequencies and percentages. Women who were alive and without recurrence were censored at the date of last follow-up in the DFS analyses. Median survival time as well as survival distribution was calculated using the Kaplan-Meier survival method, and a log-rank test was used for survival comparison. We confirmed proportionality of hazards was for all variables studied thanks to log minus log plot representation. Effects were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). HR was considered statistically significant when the 95% CI was not 1. Data were managed in an Excel database (Microsoft, Redmond, WA, USA) and analyzed using software R © (version 3.5.0), which is available online.

Results

○ Study population

Of the 1647 women with EC who received primary surgical treatment during the study period, 184 (11.2%) were ≥ 80 years old and comprised the study population. The mean age of the studied population was 84 years old (± 3.34). Eighty-six of these women had a BMI ≥ 25 kg/m² (58.9 %) and 90 had had two pregnancies or more (61.2 %). Ninety-eight had a medical history of hypertension (63.2 %), 39 of diabetes (22.7%), and 14 of breast cancer (10.4 %). Twelve of them had previously taken hormone replacement therapy (9.4%). The demographic and clinical characteristics of our population are reported in Table 1.

○ Histologic characteristics

The tumor characteristics are reported in Tables 2 and 3. Thirty-six patients (20.2%) had a non-endometrioid tumor histology. Fifty-eight (38.2%) patients were in the ESMO/ESTRO/ESGO high-risk group. LVSI was present in 55 tumors LVSI (36.7%) and myometrial invasion in 91 (58%). Out of the 184 patients, 61 (50.8%) did not undergo lymphadenectomy. Of the 59 patients (86.8%) who underwent pelvic lymphadenectomy, six (10.2%) had pelvic lymph node metastasis. Of the five patients (9.1%) who underwent paraaortic lymphadenectomy, one (20%) had paraaortic lymph node metastasis.

○ Surgical characteristics and adjuvant treatment

The surgical procedures and adjuvant treatments are reported in Table 4. Most surgeries were minimally invasive (N = 100, 57.8%), either robotic or laparoscopic. Of the 95 patients who had a formal or relative indication, 83 (45.1%) received adjuvant therapy. Overall, 69.1% patients were treated according to the standard care guidelines for EC. Fifty-three (91.4%) patients were undertreated with regards to chemotherapy. Nineteen of the 95 patients (30.2%) with a formal or relative indication of either VBRT or EBR, were undertreated.

- Survival analyses

The univariate analyses of survival (OS, DFS) are reported in Tables 1 to 4 and illustrated in Figure 1.

Five patients were excluded from OS analyses and 43 from DFS analyses because of lack of data on vital status or relapse at the time of last follow-up. Forty-nine patients were lost to follow-up (27.37 %). Thirty-three patients (25.4%) died during the follow-up period and 26 patients relapsed (18.4%).

The median follow-up of the study population was 15.27 months (range 4.85-28.79). The median OS and DFS was 16.43 months (range 6.27-24.86) and 13.55 months (range 4.49-26.6), respectively. One-year OS was 90.2 % (+/-3.2%), and 5-year OS was 49.6 % (+/-7.8%). The DFS rate at 1 year was 89 % (3.2%) and 67.7% (+/-6%) at 5 years.

The median OS was significantly lower for patients in the ESMO/ESTRO/ESGO high-risk group (HR = 3.78, 95%CI [1.28-11.36]) compared with the low-risk group, as well as in the histologic grade 3 group (HR = 2.6, 95%CI [1.07-6.3]) compared with the grade 1 group. Myometrial invasion and LVSI were significantly associated with a lower median OS (respectively, HR = 2.24, 95%CI [1.04-4.84] and HR = 3.35, 95%CI [1.44-7.79]). Inappropriate or underuse of chemotherapy was significantly associated with a lower median OS of 12.6 months [3.73-24] versus 17.3 months [7.93-41.77] when used appropriately (HR = 4.14, 95%CI [1.62-10.56]). The 5-year OS rate was 66.4 % (+/-11.5%) when the indication for chemotherapy was respected versus 27.6 % (+/-12%) (p = 0.0013). There was no statistically significant association between OS and medical history, surgical route, or respect of an indication for another adjuvant treatment in our population.

The median DFS was significantly lower in patients in the ESMO/ESTRO/ESGO high-risk group compared with the low-risk group (HR = 12.8, 95%CI [1.69-97.06]), as well as in the histologic grade 3 group compared with the grade 1 group (HR = 3.33, 95%CI [1.25-8.88]). LVSI was significantly associated with a lower median DFS (HR = 5.56, 95%CI [2.17-14.25]). In the study population, use of chemotherapy and EBR as adjuvant treatments tended to be associated with a

lower median DFS (respectively HR = 4.15, 95%CI [0.94-81.34] and HR = 2.83, 95%CI [0.99-7.99]), although not statistically significant. However, inappropriate or underuse of chemotherapy was significantly associated with a lower median DFS of 10.83 months [3.73-24] versus 17.3 months [7.93-28.5] when used appropriately (HR = 9.04, 95%CI [2.04-40.12]). The 5-year DFS rate was 88.9 % (+/-7.4%) when the indication for chemotherapy was respected versus 53.8 % (+/-10.6%) (p = 0.00044). There was no statistically significant association between DFS and medical history or surgical route.

The comparative analyses results did not change and remained statistically significant when using the ESMO/ESGO/ESTRO recommendations from 2016 (3) (see supplementary material).

Discussion

In this study, we observed that underuse of chemotherapy in spite of recommendation is associated with lower OS and DFS in the very elderly (aged 80 and over) with EC. Moreover, in this population we observed that lower OS and DFS are significantly associated with high-risk EC as defined by ESMO/ESTRO/ESGO, as well as a grade 3 histologic type and LVSI. Myometrial invasion was also significantly associated with a lower OS.

Our results show that very elderly patients with EC are less likely to receive chemotherapy and that this is associated with poorer OS and DFS rates. This inappropriate use of adjuvant chemotherapy is probably due to the presence of comorbidities in this group. Furthermore, elderly patients tend to be diagnosed with more advanced disease for which chemotherapy is indicated. However, we found that recommendation for chemotherapy was a risk factor for early recurrence whereas the actual use of chemotherapy was not. This might suggest that patients who actually receive chemotherapy when needed undergo a thorough selection process which introduces a bias in our survival results: we might indirectly be assessing the association of survival with performance status and not the treatment itself (12). Recent literature is rather clear about the fact that advanced age itself is not an independent factor for poor prognosis in EC (19), and neither is toxicity of radio- and chemotherapy (20). Nonetheless, Bishop et al observed that the use of radiation as an adjuvant treatment dropped significantly after 80 years of age (9). Clark et al showed that only 50 % of their patients aged 70 and over received the adjuvant treatment when recommended, and they found that only 30 % of them are eligible in trials due to excluding comorbidities (21). Conversely, Driver et al showed that frailty was more predictive of survival than comorbidities (22). According to Eggeman et al, these two parameters were the main reason why elderly patients were undertreated in EC management (23).

The rate of robotic surgery in our study was quite low compared to the available literature, even in the very elderly (24, 25, 26). This can be explained by the fact that our study started when robotic surgery was just beginning and that it progressively became more widespread during the study period. Furthermore, the recent literature is not consensual on postoperative complications when using minimally invasive surgery in patients with EC aged 80 and older (9, 25, 27). However,

there do not seem to be more perioperative complications in this already very fragile population (27) compared with laparotomy or a vaginal approach. Moreover, more lymphadenectomies could be performed with minimally invasive surgery when indicated with specific techniques such as the use of indomethacin green for sentinel node detection in high and high-intermediate risk endometrial cancer (18). Thus, minimally invasive surgery would appear to be highly suitable to stage fragile patients such as the very elderly to determine optimal treatment (28), without a higher risk of conversion to laparotomy (23).

Finally, the latest recommendations (18) introduce a more personalized approach with the use of molecular classification, which could also be particularly relevant in elderly patients with EC.

The proportion of elderly patients aged 80 and over in our population was similar to that observed in a North American study (11.17% vs. 10.4%, respectively) (29). Furthermore, we observed similar rates of diabetes mellitus and hypertension as in Lowe et al's population of patients aged 80 or more (27), similar proportions of stage I, II and III disease, and the same rate of patients undergoing pelvic lymph node dissection (89%). However, only 9% patients in our study underwent paraaortic lymph node dissection, versus 59% in the Lowe et al study. An American study also found LVSI and grade 3 tumors to be independent factors for recurrence in patients aged 75 and older (23).

The main strength of our study is that it is, to the best of our knowledge, the third largest sample size of women with EC aged 80 and older after Lowery et al and Wright et al with their studies on the American Surveillance, Epidemiology and End Results (SEER) population, and the biggest in France. Moreover, few European studies have focused on the very elderly patient with EC. Most studies describe patients aged 65 or 70 and older (22, 28, 31, 32), or only deal with specific histologic type or risk stage (15).

However, some limitations of this study deserve to be mentioned. Retrospective data inherently brings a classification bias. We do not know the participation rate and cannot rule out a selection bias. Our results are limited by the missing data, first concerning DFS. Nevertheless, OS seems to be a relevant endpoint in our population. Even with tumor recurrence, elderly patient might die

from other reasons than cancer. Furthermore, elderly patient could die from treatment complications or autonomy loss due to inappropriate treatment or cancer. Lastly, the elderly patients have less good clinical follow up with potential missed tumor recurrence.

Other unmeasured variables such as cancer-specific survival, geriatric assessment, quality of life and reasons for lack of treatment could yield interesting information to fine-tune our results. Indeed, frailty and geriatric assessment seem to be associated with respect towards adjuvant treatment indication: therapeutic decision changed in 21% of patients after geriatric evaluation in a previous French study (33), and up to a third of cases in an American study (23). Specific scores, such as the Geriatric Vulnerability Score (GVS), which can be used for global assessment, optimization and feasibility of chemotherapy in ovarian cancer (34), could improve treatment management. Moreover, we do not know whether chemotherapy was not performed because it was not suggested by the healthcare professionals or refused by the patients. Details on chemotherapy such as number of cycles, type and specific complications were not available in our study, which would also have been informative to look into. Finally, as European guidelines changed several times during the study period (3,17) and since (18), we can expect a chronological bias which calls for cautious interpretation of our results, despite the recent setting. We minimized this bias by performing supplementary analyses using the recommendations from ESMO/ESGO/ESTRO 2016 conference (3), which did not change our results. The latest recommendations from ESMO/ESTRO/ESGO now add tumor molecular classification (POLE or polymerase epsilon catalytic subunit gene, MSS/MSI or microsatellite instability and p53) as an indication criterion for adjuvant treatment and risk of recurrence. This would be an interesting variable to add to our study to analyze the management of EC in this population.

Conclusion

Our study adds to the available literature on the management of EC in very elderly patients. Our results on OS and DFS in this French population confirm the risk factors stated by ESMO/ESTRO/ESGO. We found that very elderly patients might be at higher risk of early death or recurrence when the indication for chemotherapy is not respected. This reinforces the recent guidelines stating that age and comorbidities should not solely define treatment strategies as this population of patients often presents high risk and aggressive tumors, which require active and global treatment. Medical staff can further support their patients by informing them that adjuvant chemotherapy can improve survival rates even after 80 years old. Other studies including tumor molecular classification, frailty, and comprehensive geriatric assessment in this specific increasing portion of older patients should take place to evaluate these findings furthermore.

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Tables and figures

Variable		Mean	Standard Deviation	OS	DFS
Age (years)		84	3.3	1.07 [0.96-1.19]	0.99 [0.87-1.14]
BMI (kg/m ²)		27.25	6	0.97 [0.91-1.04]	-
		N	%	OS	DFS
	< 18	8	5.5	Ref.	Ref.
	18 – 25	52	35.6	-	0.3 [0.03-3.33]
	> 25	86	58.9	-	1.18 [0.15-9.14]
	NA (N)	38	-	-	-
Parity	0	27	18.4	Ref.	Ref.
	1	30	20.4	1.66 [0.52-5.27]	0.38 [0.07-1.94]
	2 or more	90	61.2	1.03 [0.37-2.84]	0.90 [0.32-2.51]
	NA (N)	37	-	-	-
Hormone replacement therapy	No	116	90.6	Ref.	Ref.
	Yes	12	9.4	1.75 [0.38-8.03]	0.92 [0.12-7.07]
	NA	56	-	-	-
Hypertension	No	57	36.8	Ref.	Ref.
	Yes	98	63.2	0.96 [0.46-2]	0.47 [0.21-1.09]
	NA	29	-	-	-
Diabetes	No	133	77.3	Ref.	Ref.
	Yes	39	22.7	0.60 [0.23-1.56]	0.54 [0.16-1.82]
	NA	12	-	-	-
History of breast cancer	No	121	89.6	Ref.	Ref.
	Yes	14	10.4	1.21 [0.46-3.16]	0.56 [0.13-2.4]
	NA	49	-	-	-

Table 1. Medical history and clinical data of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) and their association to overall survival (OS) and disease-free survival (DFS) according to the Kaplan-Meier method and log-rank test (effect expressed as hazard ratio and its 95% confidence interval). NA: Not available, BMI: Body Mass Index

Variable		N	%	OS	DFS
Postoperative histology	Endometrioid	142	79.8	Ref.	Ref.
	Clear cells	8	4.5	2.44 [0.72-8.25]	5.47 [1.77-17.01]
	Serous	9	5.1	0.52 [0.12-2.23]	1.77 [0.5-6.24]
	Other*	19	10.6	1.17 [0.26-2.85]	1.86 [0.6-5.72]
	NA	6	-	-	-
Histologic grade	1	73	45.1	Ref.	Ref.
	2	40	24.7	1.69 [0.65-4.4]	1.14 [0.35-3.73]
	3	49	30.2	2.6 [1.07-6.3]	3.33 [1.25-8.88]
	NA	22	-	-	-
	II	20	13.5	1.88 [0.32-2.46]	1.38 [0.46-4.43]
	III	19	12.8	1.76 [0.63-4.91]	3.08 [1.12-8.49]
	IV	4	2.7	24.86 [3.9-158.5]	0 [0-Inf.]
	NA	36	-	-	-
ESMO/ESGO/ESTRO risk group	Low	37	24.3	Ref.	Ref.
	Intermediate	34	22.4	1.85 [0.46-7.48]	4.94 [0.51-47.59]
	High-intermediate	23	15.1	1.43 [0.26-7.93]	8.12 [0.84-78.08]
	High	58	38.2	3.78 [1.26-11.36]	12.8 [1.69-97.06]
	Advanced	0	0	-	-
	NA	32	-	-	-

Table 2. Postoperative histologic classification in FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) and their association with overall survival (OS) and disease-free survival (DFS) according to the Kaplan-Meier method and log-rank test (effect expressed as hazard ratio and its 95% confidence interval). *mixed, mucinous, undifferentiated, sarcoma. NA: Not available, FIGO: International Federation of Gynecology and Obstetrics, ESMO: European Society for Medical Oncology, ESTRO: European Society for Radiotherapy & Oncology, ESGO: European Society of Gynecological Oncology

Variable		N	%	OS	DFS
Lymph node status	Negative	50	41.7	Ref.	Ref.
	Positive	9	7.5	0.7 [0.09-5.46]	1.24 [0.14-10.65]
	Not performed	61	50.8	1.36 [0.6-3.11]	1.39 [0.44-4.39]
	NA	64	-	-	-
Myometrial invasion	No	66	42	Ref.	Ref.
	Yes	91	58	2.24 [1.04-4.84]	1.92 [0.81-4.55]
	NA	27	-	-	-
Isthmus invasion	No	94	73.4	Ref.	Ref.
	Yes	34	26.6	1.23 [0.57-2.66]	1.3 [0.53-3.19]
	NA	56	-	-	-
Lymphovascular space involvement	No	95	63.3	Ref.	Ref.
	Yes	55	36.7	3.35 [1.44-7.79]	5.56 [2.17-14.25]
	NA	34	-	-	-
Annex invasion	No	100	93.5	Ref.	Ref.
	Yes	7	6.5	1.6 [0.37-6.99]	1.8 [0.41-7.89]
	NA	77	-	-	-
Sentinel lymph node metastasis	Negative	35	89.7	Ref.	Ref.
	Positive	3	7.7	0 [0-Inf]	0 [0-Inf]
	Not performed	1	2.6	0 [0-Inf]	0.42 [0.06-3.14]
	NA	145	-	-	-
Pelvic lymph node metastasis	Negative	53	77.9	Ref.	Ref.
	Positive	6	8.8	1.11 [0.11-7.17]	1.54 [0.18-12.84]
	Not performed	9	13.3	0 [0-Inf.]	1.41 [0.17-12.20]
	NA	116	-	-	-
Paraaortic lymph node metastasis	Negative	4	7.3	Ref.	Ref.
	Positive	1	1.8	0 [0-Inf.]	0 [0-Inf.]
	Not performed	50	90.9	0 [0-Inf.]	0 [0-Inf.]
	NA	129	-	-	-

Table 3. Postoperative tumor and lymph node characteristics in FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) and their association with overall survival (OS) and disease-free survival (DFS) according to the Kaplan-Meier method and log-rank test (effect expressed as hazard ratio and its 95% confidence interval). NA: Not available

Variable		N	%	OS	DFS
Surgical route	Minimally invasive	100	57.8	Ref.	Ref.
	Vaginal	15	8.7	2.23 [0.74-6.73]	1.85 [0.48-7.04]
	Laparotomy	58	33.5	1.65 [0.73-3.71]	1.54 [0.63-3.79]
	NA	11	-	-	-
Indication for adjuvant therapy	No	37	28	Ref.	Ref.
	Yes	60	45.5	3.43 [1.14-10.29]	12.02 [1.59-91.16]
	Relative	35	26.5	1.77 [0.44-7.17]	4.88 [0.51-47.08]
	NA	52	-	-	-
Received adjuvant therapy	No	101	54.9	Ref.	Ref.
	Yes	83	45.1	0.62 [0.3-1.28]	0.9 [0.4-2.01]
	NA	0	-	-	-
Adjuvant therapy indication respected	Yes	67	69.1	Ref.	Ref.
	No	30	30.9	1.44 [0.59-3.48]	1.8 [0.65-4.95]
	NA	87	-	-	-
Indication for chemotherapy	No	71	53.8	Ref.	Ref.
	Yes	58	43.9	2.8 [1.2-6.54]	5.12 [1.7-15.44]
	Relative	3	2.3	0 [0-Inf.]	0 [0-Inf.]
	NA	52	-	-	-
Received chemotherapy	No	151	97.4	Ref.	Ref.
	Yes	4	2.6	0 [0-Inf.]	4.15 [0.94-81.34]
	NA	29	-	-	-
Chemotherapy indication respected	Yes	56	51.4	Ref.	Ref.
	No	53	48.6	4.14 [1.62-10.56]	9.04 [2.04-40.12]
	NA	75	-	-	-
Indication of radiotherapy	No	37	28	Ref.	Ref.
	Yes	60	45.5	3.43 [1.14-10.29]	12.02 [1.59-91.16]
	Relative	35	26.5	1.78 [0.44-7.17]	4.88 [0.51-47.08]
	NA	52	-	-	-
Vaginal brachytherapy	No	52	42.6	Ref.	Ref.
	Yes	70	57.4	0.65 [0.29-1.48]	2.11 [0.67-6.65]
	NA	62	-	-	-
External Beam Radiotherapy	No	80	65	Ref.	Ref.
	Yes	43	35	1.72 [0.73-4.04]	2.83 [0.99-7.99]
	NA	61	-	-	-
Radiotherapy indication respected	Yes	65	76.5	Ref.	Ref.
	No	20	23.5	2.01 [0.76-5.27]	2.03 [0.63-6.52]
	NA	99	-	-	-

Table 4. Treatment characteristics (surgical route, adjuvant treatment indication and received treatment) of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) and their association with overall survival (OS) and disease-free survival (DFS) according to the Kaplan-Meier method and log-rank test (effect expressed as hazard ratio and its 95% confidence interval). NA: Not available

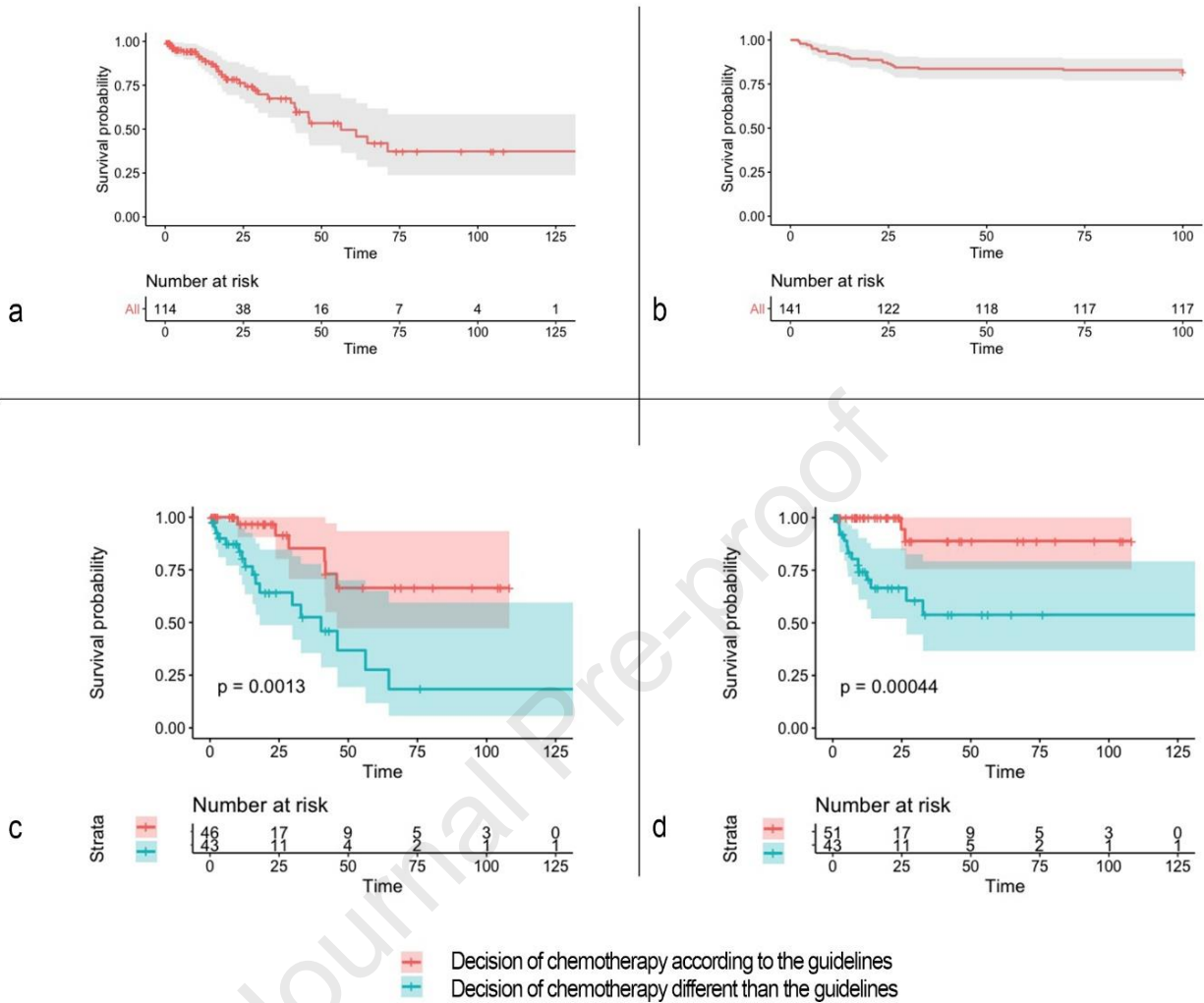


Figure 1. Survival probability graphs of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) according to the Kaplan Meier method. Time is expressed as months. a. Overall survival probability graph. b: disease-free survival probability graph. c: comparison of overall survival probability of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) according to the Kaplan Meier method and log-rank test, depending on appropriate use of chemotherapy according to the 2021 ESMO/ESTRO/ESGO guidelines. d: Comparison of disease-free survival probability of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) according to the Kaplan Meier method and log-rank test, depending on appropriate use of chemotherapy according to the 2021 ESMO/ESTRO/ESGO guidelines.

Index

EC: endometrial cancer

SENTI-ENDO: Sentinel Node Procedure and Endometrial Cancer

CNGOF: National College of French Obstetricians and Gynecologists

BMI: body mass index

FIGO: International Federation of Gynecology and Obstetrics

ESMO: European Society for Medical Oncology

ESTRO: European Society for Radiotherapy & Oncology

ESGO: European Society of Gynecological Oncology

LVSI: lympho-vascular space invasion

VBT: vaginal brachytherapy

EBRT: external beam radiotherapy

CT: chemotherapy

RT: radiotherapy

HIR: high intermediate risk

OS: overall survival

DFS: disease-free survival

SD: standard deviation

HR: hazard ratio

CI: confidence interval

Supplementary material

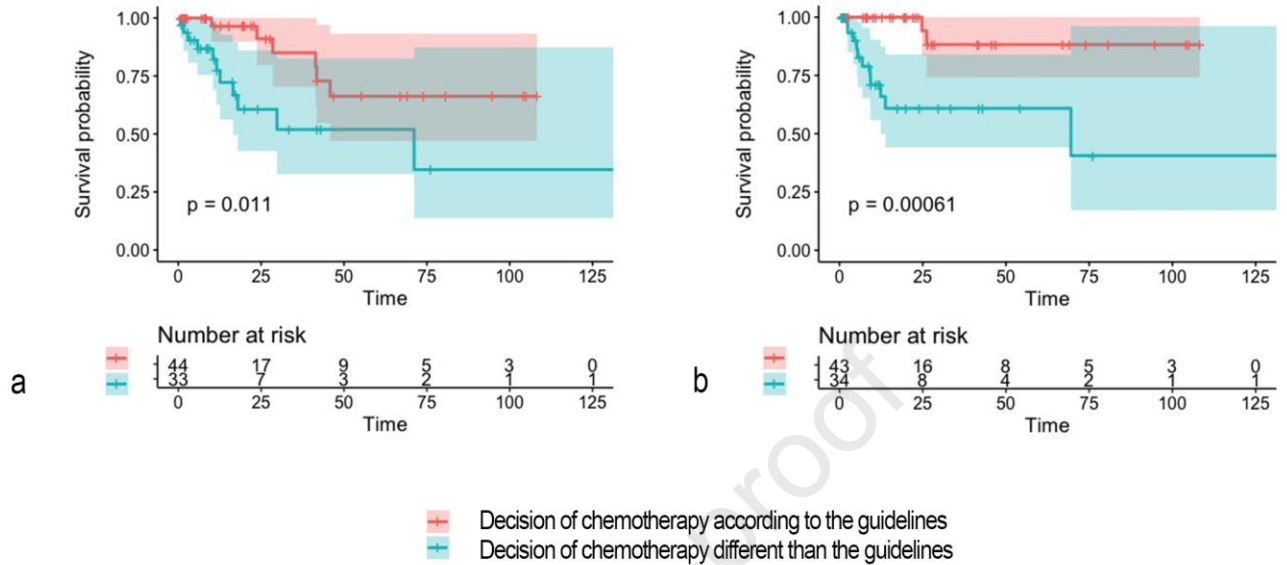


Figure S1. Survival probability graphs of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) according to the Kaplan Meier method. Time is expressed as months. a: comparison of overall survival probability of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) according to the Kaplan Meier method and log-rank test, depending on appropriate use of chemotherapy according to the 2016 ESMO/ESTRO/ESGO guidelines. b: Comparison of disease-free survival probability of FRANCOGYN patients with endometrial cancer aged 80 or older (N=184) according to the Kaplan Meier method and log-rank test, depending on appropriate use of chemotherapy according to the 2016 ESMO/ESTRO/ESGO guidelines.

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FRANCE

01/07/2022

Dear Riccardo A. Audisio,

I wish to submit an original research article entitled "ENDOMETRIAL CANCER OF THE VERY ELDERLY: MANAGEMENT AND SURVIVAL IN THE FRANCOGYN POPULATION" for consideration by the European Journal of Surgical Oncology.

Present work is original and has not been published elsewhere, nor currently under consideration for publication elsewhere.

I have no conflicts of interest to disclose.

Thank you for your consideration of this manuscript.

Sincerely,

Flore-Anne MARTIN