

Impact of age on the quality of care in endometrial cancer: a retrospective study of 145 patients

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Summary

Objectives: Endometrial cancer is the fourth most common cancer and affects mostly the elderly. Advanced age is a poor prognostic factor but reasons are numerous and controversial. The objective of this study was to characterize the effect of age on endometrial cancer patients medical care. **Materials and Methods:** It was a descriptive and comparative study of a retrospective cohort of 145 patients having received care for endometrial cancer during ten years in the Gynecological Department of Saint-Etienne Hospital. The 145 patients studied were subdivided into three groups according to their age at diagnosis: < 70 (group 1), 70-79 (group 2), and > 80 (group 3). The data collected were: clinical characteristics; preoperative, operating and pathological data, and postoperative care. For each patient, the authors evaluated compliance to patient management guidelines. **Results:** Postmenopausal bleeding was the most common reason of first consultation and incidental diagnoses were more frequent in group 2 (13.8%). Concerning FIGO staging, there was an over-representation of Stages III and IV in group 1, while the distribution was more in favor of Stages I and II for older patients groups. No para-aortic lymphadenectomy was performed in patients from group 3 despite seven theoretical indications. This non-compliance to guidelines was detected in two-thirds of patients in group 3. **Conclusion:** Elderly patients from the present cohort showed less aggressive and advanced tumors compared to younger patients. Yet, they did not receive optimal surgical and adjuvant therapy according to guidelines. A multidisciplinary evaluation using standardized assessment is needed in order to help physicians in the decision-making process.

Key words: Elderly patients; Gynecologic oncology; Endometrial cancer.

Introduction

Endometrial cancer is the fourth most common cancer and the first most frequent pelvic cancer in women in developing countries with an incidence of 14.7 per 100,000 women in 2012 which is steadily increasing [1]. The expected aging of the population will lead us to take care of patients becoming older and therefore more fragile and more vulnerable to disease and treatments to implement [2]. Several studies have shown that advanced age is a prognostic factor associated with shorter survival [3–11]. Yet, no threshold can be clearly defined [5–8, 12]. This threshold varies from 60 to 80 years depending on the authors [5, 6, 9–11]. Factors responsible for this poor survival are numerous and controversial: influence of associated comorbidities, more “aggressive” tumors, delayed diagnosis, and/or undertreatment. Other authors do not find this pejorative effect of age at diagnosis on survival [11, 13]. Due to uncertainties about the influence of age, the objective of this study was to characterize, with a descriptive and comparative analysis of three groups of patients, the effect of age on endometrial cancer patients’ medical care throughout diagnosis, surgery, and adjuvant therapy.

Materials and Methods

It was a descriptive study of a retrospective cohort based on all consecutive patients having received care for endometrial cancer between January 2002 and January 2012 in the Gynecological department of Saint Etienne University Hospital, Saint-Etienne, France. During this period, 172 patients were eligible from pathology laboratory register of the hospital; 27 were excluded from the analysis due to insufficient data.

Clinical characteristics collected were: comorbidities (hypertension, diabetes, hypercholesterolemia, cardiovascular disease, and other notable medical conditions), body mass index, parity, age at menarche, age at menopause, and intake and duration of hormone replacement therapy.

Preoperative data collected were age and symptoms at the time of diagnosis, realization of a biopsy of the endometrium (date, technique used) and its result, and realization of a neoadjuvant treatment (date and nature).

The operating data, collected from medical, operative, and anesthesia records were: date of surgery, surgical approach (sub umbilical midline incision, Pfannenstiel incision, laparoscopy or vaginal), hysterectomy, salpingo-oophorectomy, realization of a pelvic and/or para-aortic lymphadenectomy, operating time, and length of hospital stay.

Pathological data collected were: histological type, diagnostic concordance with preoperative histology, histological grade, myometrium infiltration (%), uterine isthmus involvement, endocer-

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Table 1. — *Clinical characteristics cohort.*

	Group 1 (n=41)	Group 2 (n=65)	Group 3 (n=39)	<i>p</i>
Diagnostic age (years)	63.7	73.8	84.7	
<i>Range</i>	33-69	70-79	80-94	
Body mass index (BMI) kg/m ² , mean ± SD	29.1 ± 8.7	27.6 ± 4.9	25.9 ± 4.7	NS
<i>Range</i>	19.9-53.3	18-40.4	18.7-39.7	
Parity (mean)	1.98 ± 1.88	2.52 ± 1.85	2.13 ± 1.88	NS
<i>Range</i>	0-9	0-8	0-8	
Age of first menarche, years (mean)	12.8	13.2	12.7	NS
<i>Range</i>	11-15	11-18	11-15	
Age at menopause, years (mean)	50.8	53.2	50.1	NS
<i>Range</i>	42-59	39-59	42-56	
Hormone replacement therapy n (%)	7 (17)	4 (6.1)	0	NS
<i>Length in years</i>	7.86	9	0	
Hypertension n (%)	16 (39)	46 (70.8)	27 (69.2)	<i>p</i> < 0.05
Diabetes n (%)	10 (24.4)	19 (29.2)	5 (12.8)	NS
<i>Non insulin-dependent diabetes n(%)</i>	8 (80)	14 (73.6)	2 (40)	
Hypercholesterolemia n (%)	7 (17)	16 (24.6)	11 (28.2)	NS
Cardio-vascular diseases n (%)	10 (24.4)	26 (40)	17 (43.6)	NS
<i>Thrombosis, pulmonary embolism, cerebrovascular accident</i>	6	14	8	
<i>Angina - myocardial infarction</i>	1	6	5	
<i>Other</i>	3	6	4	
Previous cancer n (%)	7 (17.1)	12 (18.5)	12 (30.8)	NS
Number of comorbidities: association of risk factors (hypertension, hypercholesterolemia, diabetes, and cardiovascular diseases were grouped from 0 (no risk factor) to 4 (all risk factors)); mean ± SD	1.04 ± 1.13	1.64 ± 1.06	1.53 ± 0.97	<i>p</i> < 0.05
<i>Range</i>	0-4	0-4	0-3	

n=number of patients, *NS*=non significant, *SD*=standard deviation.

vical involvement, presence of lymphovascular emboli, number of nodes present in the pelvic and para-aortic lymphadenectomy, lymph node status, and presence of malignant cells in the peritoneal cytology. Staging was determined according to the International Federation of Gynecology and Obstetrics (FIGO) classification 2009 for all the present patients, including patients operated before that date.

Postoperative care data were also collected in case of adjuvant therapy: chemotherapy starting date, chemotherapy regimen, number of chemotherapy cycles completed; start and end dates of pelvic radiotherapy, and/or brachytherapy.

For each patient, the authors described the overall care (neoadjuvant, adjuvant, and surgical care) and evaluated the compliance to regional guidelines. "Compliance" to regional guidelines was defined as a therapeutical approach (type of surgery procedure, adjuvant therapy) in agreement with guidelines and "non-compliance" was defined as alternative therapeutical strategies.

The 145 patients studied were subdivided into three groups according to their age at diagnosis: under 70 (group 1), 70-79 years (group 2), 80 or more (group 3). A descriptive and comparative analysis of the three groups about clinical and histological data was performed.

Statistical analyzes were carried out with SAS version 9.2. For continuous numerical variables, means are given with standard deviation (± SD). Categorical variables were compared by the Chi 2 test or Fisher's exact test when appropriate. The average differences between continuous variables were analyzed by Student's *t*-test. A *p* value ≤ 0.05 was considered statistically significant. This study was accepted by an ethics committee on 10/02/2016.

Results

Epidemiological characteristics are shown in Table 1. In the present cohort, the mean age at diagnosis was 73.9 years, range (33-94). Forty-one patients belonged to group 1, 65 patients belonged to group 2, and 39 patients belonged to group 3. Among the risk factors for endometrial cancer, only hypertension was significantly more frequent in older patients (*p* < 0.05). Hypercholesterolemia and cardiovascular disease increased with age. Younger patients had a lower average number of comorbidities than patients aged ≥70 (1.04 vs. 1.64, *p* < 0.05).

Presenting symptoms in the present cohort were: postmenopausal bleeding, deep vein thrombosis, impaired general status, pain, and incidental diagnosis during non-oncological hysterectomy indications like prolapse surgery (n=10). Postmenopausal bleeding was the most common reason of first consultation for 90.2% and 94.9% of patients of group 1 and 3, respectively, compared to 81.5% in group 2. Incidental diagnoses were more frequent in group 2 (9 cases or 13.8%, *p* < 0.05).

More than half of the present patients underwent hysteroscopy with biopsy curettage (57.2%). The simple endometrial biopsy (Pipelle de Cornier) was carried out in 24% to 35% of cases; this proportion increased progressively with age. Biopsy was not performed in 12% of cases

Table 2. — Surgical procedures.

	Group 1	Group 2	Group 3	
Surgical approach, n (%)				$p < 0.001$
Sub umbilical midline incision	18 (43.9%)	21 (32.3%)	6 (15.3%)	
Pfannenstiel incision	5 (12.2%)	7 (10.7%)	9 (23.0%)	
Laparoscopy	14 (34.1%)	29 (44.6%)	10 (25.6%)	
Vaginal	4 (9.7%)	7 (10.7%)	5 (12.8%)	
No surgery	0	1 (1.5%)	9 (23.0%)	
Total hysterectomy, n (%)	40 (97.6%)	63 (96.9%)	30 (76.9%)	NS
Salpingo-oophorectomy, n (%)	36 (87.8%)	8 (90.8%)	29 (74.4%)	NS
Pelvis node dissection, n (%)	31 (75.6%)	49 (76.5%)	16 (53.3%)	$p = 0.05$
Para-aortic node dissection, n (%)	6 (14.6%)	10 (15.6%)	0	$p < 0.05$

n=number, *NS*=non significant.

Table 3. — Average length of surgery and of hospital stay.

	Average length of surgery (minutes ± SD)		Average length of hospital stay (days ± SD)	
<i>Age (years)</i>		NS		NS
Group 1	160.1 ± 63.1		7.45 ± 5.63	
Group 2	157.5 ± 72.6		7.13 ± 4.70	
Group 3	113.3 ± 52.9		7.90 ± 4.24	
<i>Surgical approach</i>		$p < 0.001$		$p < 0.001$
Sub-umbilical laparotomy	131.1 ± 64.2		10.71 ± 5.31	
Pfannenstiel	147.3 ± 54.1		8.65 ± 4.38	
Cœlioscopia	183.7 ± 62.3		4.52 ± 2.09	
Vaginal	76.8 ± 32.0		6.56 ± 5.21	
<i>Pelvis node dissection</i>		$p = 0.003$		NS
Yes	170.5 ± 64.3		9.08 ± 6.89	
No	91.0 ± 36.4		6.72 ± 3.60	
<i>Pelvis and para-aortic node dissection</i>		$p < 0.001$		NS
Yes	255.3 ± 29.6		7.67 ± 5.08	
No	134.5 ± 58.6		5.21 ± 1.84	

NS=non significant, *SD*=standard deviation.

for groups 1 and 2 compared to 5% for group 3 ($p = 0.55$).

There was a discrepancy between the preoperative and definitive histology in 24.6% of cases with upper tumor grade re-evaluation or diagnosis of a different histological type. No difference was found between Pipelle de Cornier and hysteroscopy (Table 2).

Histological type 2 was more common in patients in group 1 (46.34% against 26.56% and 33.33% for groups 2 and 3) without a significant difference ($p = 0.113$).

There was no significant influence of age on histological grade, although there were more high-grade tumors in patients in groups 1 and 2 (26.7% and 27.3% against 11, 5% in group 3). No significant influence of age was found for myometrial invasion ($p = 0.37$), presence of lymphovascular emboli ($p = 0.84$), and cervical stroma invasion. The number of lymph nodes removed in case of pelvic and/or para-aortic node dissection was also independent of age. Node metastasis (N1) was higher in group 1 (18.2%) than in groups 2 and 3 (respectively, 12.2 and 12.5%). This difference was not significant.

Concerning FIGO staging, there was an over-representation of Stages III and IV in group 1, while the distribution was more in favor of Stages I and II for older patients groups ($p < 0.05$). These data are reported in Figure 1.

Peritoneal cytology was not carried out in 10% to 15% of operated patients. When carried out, negativity was seen in 70% to 83% of cases. There was no significant difference between the three groups ($p = 0.28$).

Ten patients had not been surgically treated: one from group 2 (cardiovascular contraindication), nine in group 3 (seven refusal by the patient or his family because of dementia, two anesthesia contraindication because of terminal renal insufficiency, leukemia, and severe cardiovascular history).

The sub-umbilical midline incision was the most common surgical approach for patients in group 1 (43.9%), while laparoscopy was preferred for group 2 (45.31%). For the oldest old (group 3), laparoscopy and Pfannenstiel incision were the two preferred surgical approaches (30% and 33.33%) ($p < 0.05$).

Table 4. — Compliance to regional guidelines for the surgical and adjuvant management.

	Group 1 (n=41)	Group 2 (n=65)	Group 3 (n=39)
Non-compliant surgical management (n)			
No surgery	0	1	9
Incomplete node staging	7	9	10
Non-compliant adjuvant therapy	7	14	7
Total n (%)	14 (34.1)	24 (36.9)	26 (66.7)

n=number

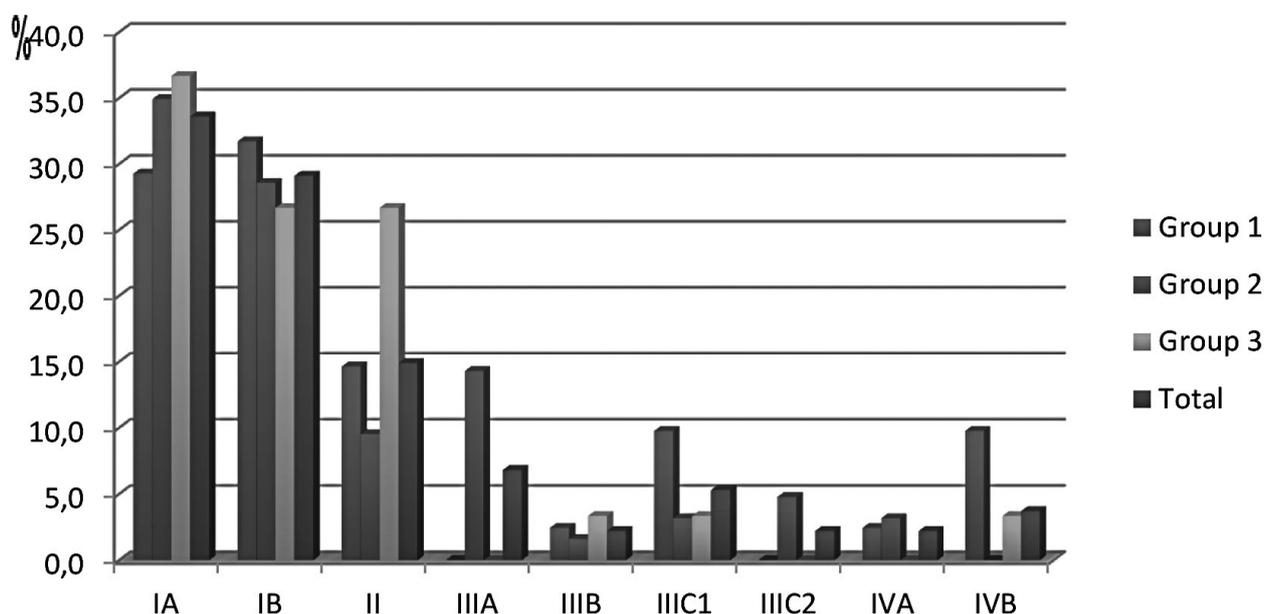


Figure 1. — FIGO stage distribution depending of age at diagnosis

Pelvic lymphadenectomy was carried out in 75% of cases for groups 1 and 2, but only in 53% for group 3 ($p = 0.05$). The para-aortic lymphadenectomy was performed in 15% of patients operated, all from groups 1 and 2; no para-aortic lymphadenectomy was performed on patients from group 3 despite seven theoretical indications ($p < 0.05$). Surgical procedures are summarized in Table 2.

In multivariate analysis, the average duration of the intervention varied significantly depending on the surgical approach and the achievement of pelvic and/or para-aortic node dissection ($p < 0.05$). Age did not influence the operating time.

Length of stay was correlated with the surgical approach, regardless of the type of surgery or the realization of a lymph node dissection ($p < 0.001$). Age did not influence length of stay. All data concerning operating time and length of hospital stay are summarized in Table 3.

Two-thirds of patients in groups 1 and 2 received adjuvant therapy (chemotherapy, external radiotherapy, and/or brachytherapy) compared to one-third of patients in group 3 ($p = 0.004$). In the subgroup of type 2 tumors, age was significantly associated with the realization of adjuvant therapy ($p < 0.05$).

Compliance to regional guidelines was poor for almost half of the present patients, with significant differences between the three groups. Reasons for non-adherence concerned surgery management (absence of surgery, type of hysterectomy performed, absence of pelvic and/or para-aortic lymph node biopsy or dissection), and adjuvant therapy (no adjuvant therapy, incomplete irradiation). This non-compliance to guidelines was detected in 35% of patients in groups 1 and 2, versus two-thirds of the patients in group 3 ($p < 0.05$). These data are summarized in Table 4. In groups 1 and 2, histological tumor type was not associated with compliance to guidelines. In group 3, nearly 53% of non-compliance was seen in type 2 tumors.

Discussion

The present authors conducted a French monocentric study in order to identify the impact of age on endometrial cancer management. The present sample was well balanced between groups in terms of clinical characteristics and endometrial cancer risk factors, such as estrogenic exposure duration, body mass index, diabetes, hypercholesterolemia, and cardiovascular disease. The only risk factor signifi-

cantly increased in patients over 80 years was hypertension. Obviously, comorbidities significantly increase with age as reported in literature [14, 15]. No differences were found on preoperative management. However, there were a significant number of incidental findings in group 2 when operated for surgical prolapse correction. Indeed, this group is most affected by this kind of surgery [16]. There was no difference in terms of preoperative histological diagnosis or symptoms between groups 1 and 3. Postmenopausal bleeding was the most frequent symptom at diagnosis.

The present authors have shown that there was no significant difference between their three groups in terms of histological type, although type 2 tumors were more frequent in younger patients. However, they report a great proportion of type 2 tumors in this cohort, which is different from usual data reported in the literature: up to 15% to 20% of cancers of the uterus in the largest series, versus 26.6% in group 2 to 43.3% in group 1. The age and the history of pelvic radiation are known to be the main risk factors [17, 18] for this kind of tumor. Yet, none of the present patients with a type 2 tumor had been irradiated. Surprisingly, the authors found a rather beneficial effect of age on tumor histology and aggressiveness, which is in contrast with literature. They found in fact, less higher Stages (III or IV) in patients over 80 years compared to younger patients, with, however, a higher proportion of Stage II tumors. Gayar *et al.* showed that FIGO stages and histological grades were higher in patients over 75 years with localized endometrioid carcinoma (Stage I or II according to the 1988 classification) [19]. However, no advanced stages were included in this study. Conversely, Fleming *et al.*, also evaluating localized endometrioid cancers, did not find an effect of age on tumor aggressiveness [13]. For Stages III and IV, Lachance *et al.* showed that elderly patients had more aggressive tumors with higher grades compared to younger patients [20]. However, the “cut-off” in terms of age was 65 in this study, which can affect results. In a more recent study comparable to the present study, Ouldamer *et al.* did not find differences in stage distribution (FIGO 2009) between two groups of patients (65-79 years and 80 and over) [11]. Although some authors explain the excess mortality related to cancer in the elderly by more aggressive tumors, the present authors did not find significant differences between the three groups concerning histological grades and other prognostic factors [19, 21].

Concerning surgical management, nearly a quarter of patients in group 3 was not operated. In contrast, only one patient in groups 1 and 2 has been refused to surgery ($p < 0.05$). Indeed, elderly patients often present many comorbidities rendering them inoperable. The present authors retrieved less median laparotomy in group 3, in favor of Pfannenstiel incision or vaginal surgery, which are better tolerated approaches ($p < 0.001$). There was also a smaller proportion of laparoscopies in patients over 80 years (25.6%), although the latter is above the national averages

for the same period: rates below 10% in similar studies [9, 22, 23]. During this decade, laparoscopy has become the reference surgical approach for the staging of endometrial cancer [24–26]. It requires more time and a higher operating cost, but allows faster rehabilitation, with a significantly reduced length of hospital stay [27]. In the present series, age was not a factor influencing the operative time and length of stay. This might be explained by the different surgical approach used according to patient’s health status. Regarding lymph node involvement, at equal stage, the present authors have shown that older patients were receiving less para-aortic dissection than younger counterparts. Moreover, no node dissection was performed in patients over 80 years. This sub-optimal management in older patients is also an important point that can influence survival. As shown by Huang *et al.* survival is significantly influenced by the realization of lymphadenectomy from Stage IB in case of histological factors of poor prognosis [28, 29].

In the present population younger patients had more aggressive tumors with poorer prognosis (type 2, FIGO Stages III and IV), while patients over 80 years had conversely, tumors with a better prognosis, (type 1, FIGO Stages I and II). However, older patients received less node dissection and may have been understaged. Indeed, some authors reported with increasing age, nodal involvement increase [30]. However Aletti *et al.* showed in ovarian carcinoma an impact of age (≥ 75 years) on morbidity and postoperative mortality. However, they did not establish a relationship between, on the one hand the age and overall survival, and on the other hand, the risk of complications and achieving a para-aortic lymphadenectomy in these elderly patients [31]. On the whole, benefits and risks of pelvic and para-aortic dissection must be well balanced in older patients in order to apply the best therapeutic strategy.

Concerning adjuvant management of patients, the present authors have shown that older patients received less frequently adjuvant therapy regardless of modalities (chemotherapy, radiotherapy, and brachytherapy), with a significant effect mainly in type 2 tumors, while they require a more aggressive adjuvant care, comparable to ovarian cancers. This element may be explained by the sub-staging of older patients due to less para-aortic lymphadenectomy. This undertreatment is not justified as the PORTEC trial has shown no significant difference in terms of tolerance of external radiotherapy depending on age, while there is a beneficial effect on locoregional disease control [6, 32].

Finally, the present authors have seen that the undertreatment of patients over 80 years concerns almost 50% of them (18 of 39 patients). Non-optimal treatment is mainly explained by refusal or contraindications to surgery, incomplete surgical staging, refusal, contraindications to radiotherapy, and poor tolerance to chemotherapy. These data are consistent with existing literature [33].

One major limitation of the present study is that the authors only considered chronological age. They did not take into account the diversity and heterogeneity of geriatric population. Indeed, due to collection of retrospective data, they did not report geriatric covariates such as functional status, psycho-cognitive status, nutritional status, medication, and social support. Therefore, they did not evaluate the impact of different stages of aging and frailty on patterns of care in endometrial cancer. However, they subdivided elderly patients in two groups, one older than 70 and the other one older than 80, which is usually regarded by geriatricians as a cut-off for the oldest, and are considered to be intrinsically frail patients [34]. Another limitation of the present study is represented by the lack of follow-up which did not allow any analysis in terms of recurrence or survival. Therefore, no analysis on whether undertreatment is a risk factor for poor prognosis could be performed although literature data seems to suggest there is a relation. Selection bias was controlled including all consecutive patients in the present center.

No standardized evaluation of older patients before surgery was reported in the present cohort. In the future, the preoperative assessment of cancer in the elderly (PACE) will represent a useful tool in evaluating patients' fitness for surgery and may decrease undertreatment in this population. It should be routinely used in clinical practice along with a comprehensive geriatric assessment [35].

Conclusion

In conclusion, patients over 80 years of age from the present cohort showed less aggressive and less advanced tumors compared to younger patients. Older patients did not receive optimal surgical and adjuvant therapy according to known guidelines. In this study, poor prognosis of endometrial cancer in this patient population might therefore be explained more by undertreatment rather than by more aggressive tumors. The older patients are the most vulnerable group in terms of comorbidities, but age should not be the main criteria to decide whether or not we should perform a therapeutic strategy. A multidisciplinary evaluation using standardized assessment is needed in order to help physicians in the decision-making process. An evaluation of these practices and consequences on the care of older patients will be needed in the coming years.

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