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1 **Endometrial cancer in elderly women: which disease, which surgical management? A**
2 **systematic review of the literature**

3

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24 All authors have no conflict of interest.

25

26 ABSTRACT

27

28 **Objective:** Endometrial cancer primarily affects elderly women. The aim of the present
29 literature review is to define the population of elderly women with this disease and to define
30 the characteristics of this cancer in elderly people as well as its surgical treatment.

31 **Materials and Methods:** A systematic review of the English-language literature of the last 20
32 years indexed in the PubMed database.

33 **Results:** Endometrial cancer is more aggressive in elderly women. However, surgical staging
34 performed in elderly patients is often not concomitant with the disease's aggressiveness in this
35 group. Mini-invasive surgery is performed less often, for no obvious reason. Of note,
36 oncogeriatric evaluation was not usually ruled out to determine the most appropriate surgical
37 modality.

38 **Conclusion:** Studies are needed to evaluate surgical management of endometrial cancer in
39 elderly women, notably with the aid of oncogeriatric scores to predict surgical morbidity.

40

41

42 **Key words:** elderly women, endometrial cancer, oncogeriatric scores, surgical approach

43

44 Authors have no conflict of interest.

45

46

47 INTRODUCTION

48

49 Endometrial cancer is a disease primarily affecting elderly women: the mean age at
50 diagnosis is 68 years (1). The current population is getting older, so the incidence of the
51 disease and also its management are set to increase in the coming years. Anyone who takes an
52 interest in this disease in the specific subpopulation formed by elderly women will notice it
53 has features specific to this age group. The aim of the present literature review is to define
54 which kind of endometrial cancer was found in elderly, how to define elderly and to focus on
55 the surgical management performed and complications in elderly. In addition, we describe the
56 feasibility and value of managing the disease in this age group using a mini-invasive approach
57 (laparoscopic or robotic).

58

59

60

61 MATERIALS AND METHODS

62 Inclusion criteria were studies that included adult females with either age more than 65 years
63 old and endometrial cancer with surgery. Exclusion criteria were patients with recurrent
64 endometrial cancer, studies with no inclusion of women older than 65 years, duplicate data.
65 Because of lack consensus of elderly woman definition in literature, authors researched also
66 geriatric tools in order to define frailty. Inclusion criteria for this search were “oncologic
67 score”.

68 The primary outcomes were rate of post-operative complications (morbidity and mortality),
69 histo-pathological analysis of uterus and nodes and survival rate. The secondary outcome was
70 described oncogeriatric scores nevertheless kind of cancer.

71 Original studies, meta-analyses and reviews published in English and French were
72 considered. In case of duplicate publications from the same team, the most recent study was
73 included. Case reports were excluded. Two investigators (CB and VL) independently
74 extracted the data from the remaining studies. Finally, all the authors scrutinized relevant
75 studies and a decision made on their inclusion in the review.

76 The bibliographic search was carried out for the period covering the last 20 years (January,
77 1995 to January, 2015). The following sources were explored:

78 - Medline: PubMed (the Internet portal of the National Library of Medicine)

79 <http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed>

80 - Central Cochrane Library

81 - EmBase

82 - National Institute on Aging

83 <http://www.nia.nih.gov/sites/default/files/>

84 - INSEE: *Institut National des Statistiques et des Etudes Economiques*

85 <http://www.insee.fr/fr/themes/document>

86 The authors used various key words, alone or in combination, to produce maximum results
87 during the literature search. The following key words were used: elderly women, older,
88 frailty, laparoscopy, laparotomy, vaginal hysterectomy, surgery, recidive, specific survival,
89 morbidity, endometrial carcinoma, endometrial cancer, oncogeriatric score. To minimize the
90 possibility of duplication, all key fields of a particular study were downloaded including
91 unique identifier (e.g. PMID), digital object identifier (DOI), clinical trial number (from

92 www.clinicaltrials.gov), abstract and key words. The initial citations were then merged into
93 one file using the Endnote software and duplicate results were removed. The title of each
94 study was individually reviewed by designated authors to identify the studies addressing the
95 research question. Thereafter, abstracts of selected studies were reviewed according to the
96 predefined inclusion and exclusion criteria and irrelevant studies were removed. Studies
97 meeting all inclusion and exclusion criteria were selected for full-text review and data
98 extraction.

99

100

ACCEPTED MANUSCRIPT

101 RESULTS

102

103 The electronic database literature search identified 25635 articles on endometrial
104 cancer of which 2117 were about surgical staging and only 16 with detailed data about
105 women older than 65 years old. Authors identified only two studies that assessed
106 oncogeriatric score for surgery, of which only one dealt with gynecologic oncology (2)(3).

107 There is a lack of consensus in the definition of elderly and consequently there is a high
108 heterogeneity of the published data to clearly review the subject.

109

110 What is an elderly woman?

111

112 In order to optimise the surgical management of elderly patients, it is important to
113 better define what an elderly patient is, especially in surgery, and notably which of these
114 elderly patients are at risk of complications.

115 There is no consensus in the current literature as regards the definition of “elderly woman”,
116 variously described as being over 63, 65, 70 or 75 years. Defining what constitutes an old
117 person is a complex issue. One of the commonly used criteria is age, with the threshold age
118 set at 65 years by the WHO (4) and the INSEE (5), and 75 years by the InCA (*Institut*
119 *National du Cancer*). Another criterion, more socioeconomic, is to consider elderly as people
120 who are no longer working. Hence, age is not a good way of predicting postoperative
121 complications. Although not as straightforward to apply as age, vulnerability, frailty and
122 dependence are better able to detect people to manage geriatrically and who are at risk of
123 complications. Hence old age is not defined in relation to a specific age but rather as a state of
124 functional incapacity, whether subjective or objective. The concept of frailty, today adopted
125 by geriatricians, corresponds to a reduction in physiological reserves limiting the patient’s
126 capacity to respond to a stress and predisposing him/her to adverse events. It corresponds to a
127 phenotype found in patients living in an institution, who have an excess risk of falls,
128 hospitalisation, or other adverse events (6). As mentioned above, the population is getting
129 older and life expectancy is increasing considerably. According to the INSEE, the life
130 expectancy at 65 years for a woman is currently 23 years, while expectancy of life in “good
131 health” at 65 years is 9 years (7). In relation to the topic we are interested in, surgery, the
132 notion of good health is a very important one.

133 Even though a definition of elderly in the field of surgery is lacking, it will be accepted
134 that such a person has fewer physiological reserves to respond to the stress of a surgical
135 procedure (anaesthesia, perioperative bleeding) or postoperative complications. So, in elderly
136 people, more important than the rate of complications is that when a complication occurs
137 postoperatively, it is less well tolerated and causes a chain reaction of other complications.
138 Furthermore, elderly people may present complications specific to their age (e.g. confusion,
139 falls, etc.), while so-called “classic” postoperative complications may have atypical
140 presentations that the physician must be able to diagnose (8). In this context, new
141 oncogeriatric scores are being used to better detect elderly people at risk of complications and
142 those who would benefit from optimal medicosurgical treatment.

143

144 *Oncogeriatric scores*

145

146 The goal is to perform a comprehensive geriatric assessment (CGA), encompassing
147 the somatic, functional and psychosocial domains, to provide an objective evaluation of the
148 health status of the elderly person, so that a multidisciplinary care plan may be devised. The
149 CGA uses several scores such as the MNA (Mini Nutritional Assessment), the ADL (Activity
150 of Daily Living) and IADL (Instrumental Activity of Daily Living) that evaluate dependence,
151 the MMSE (Mini Mental State Examination), the CIRS-G (Cumulative Illness Rating Scale
152 for Geriatrics) evaluating comorbidities (9). The “timed get up and go test” (TUG) evaluates
153 the risk of a fall, the VES-13 (Vulnerable Elders Scale) evaluates survival and decline and the
154 GDS (Geriatric Depression Scale) evaluates depressive symptoms. A literature review
155 involving 51 publications showed that frailty, nutritional status and comorbidities are
156 predictive of all-cause mortality. Frailty is predictive of chemotherapy toxicity; cognitive
157 impairment and a reduction in the ADL are predictive of chemotherapy discontinuation;
158 reduction in the IADL is predictive of perioperative complications (10). The authors of the
159 review express their reservations as to the validity of these tests, given that the studies are too
160 heterogeneous to guide clinical decisions. Regardless of the issue of heterogeneity, the
161 reference oncogeriatric evaluation test, the MGA (Multidimensional Geriatric Assessment),
162 consisting of 7 items (MNA, TUG, ADL, IADL, MMSE, GDS and CIRS-G), takes a long
163 time to administer, such that, despite the recommendations of the International Society of
164 Geriatric Oncology (SIOG), level of use is very low. Currently, the scientific community
165 believes that for a test to be acceptable, it must take about 10 minutes of the practitioner’s

166 time. With this in mind, the G8 tool was developed to identify patients who should undergo a
167 geriatric evaluation. G8 consists of 8 items and its validity was recently assessed in a large,
168 multicentre study (ONCODAGE), which showed that it takes an average of 5 minutes to
169 complete it, it is more sensitive than VES-13 ($p=0.004$) and that an abnormal score ($\leq 14/17$)
170 is predictive of 1-year survival ($p=0.0001$). At the present time, G8 seems to be one of the
171 best tools for detecting elderly patients who should undergo a geriatric evaluation (11). The
172 current literature does not provide a specific score to evaluate perioperative risks in elderly
173 people with cancer. Possibly because they are under-represented in clinical trials (12) (13),
174 making their management even more difficult. Nevertheless, some studies have used existing
175 oncogeriatric scores to evaluate this risk. Among these, a prospective study by the SIOG
176 evaluated an extension of the CGA, the PACE (Preoperative Assessment in Elderly Cancer
177 Patients), for its ability to assess the suitability of elderly cancer patients for surgery. This
178 study used the MMS, ADL, IADL, GDS, BFI (Brief Fatigue Inventory), ECOG performance
179 status (PS), ASA (American Society of Anesthesiology) scale and SIC (Satariano's Index of
180 Comorbidities). Results showed that the IADL, fatigue and PS were associated with a 50%
181 increase in the relative risk of postoperative complications ($p<0.05$). On multivariate analysis,
182 this study identified moderate to severe fatigue, the IADL and the PS as factors predictive of
183 postoperative complications ($p<0.05$). Finally, deterioration of IADL and PS were associated
184 with a longer hospital stay ($p<0.05$) (14). Independently of oncogeriatric scores but
185 specifically in oncogynaecology, a retrospective Italian study evaluated perioperative
186 morbidity and mortality in patients aged over 70 years as a function of the ASA score. It
187 found a higher rate of postoperative complications in ASA III/IV patients than in ASA I/II
188 patients ($p \leq 0.001$) (15). There is no consensus regarding the definition of frailty. However
189 Makary *et al.* established a frailty scale based on 5 criteria: weakness, weight loss, exhaustion,
190 low physical activity and slow walking speed. This scale was tested in a prospective surgical
191 study and was found to predict postoperative complications, length of hospital stay and
192 placement in an institution of elderly people (2). In the specific domain of gynaecological
193 surgical oncology, it has been established that preoperative frailty in elderly women is
194 predictive of postoperative morbidity (postoperative complications and rehospitalisation
195 within 30 days) (3). The score uses 5 variables that were previously validated by Fried *et al.*
196 as defining frailty (6): weight loss, reduction in grip strength, exhaustion, low physical
197 activity and slowing of walking speed. Each variable is rated as 0 or 1. According to the
198 frailty index, patients are classified as non-frail (0–1), intermediate-frail (2–3) or frail (4–5).
199 Although this scale performs better than usual scores (ASA, ECOG, Charlson Comorbidity

200 Index) (2) (16), it is still too time-consuming (approximately 20 min). As the only existing
201 tool for evaluating frailty in elderly women in the specific field of gynaecological oncological
202 surgery, other studies are necessary in order to improve it and make it more practical.

203

204 Characteristics of endometrial cancer in elderly women

205

206 *Epidemiology*

207

208 In terms of incidence, endometrial cancer ranks number 4 among women, with 7,200
209 new cases per year in 2012 in France (InVS: *Institut National de Veille Sanitaire*) and it is the
210 5th most common cause of cancer mortality in women. It primarily occurs after the
211 menopause, with a mean age of 68 years at diagnosis. The relative 5-year survival rate is 76%
212 overall, increasing to 95% for localised early stages. With the aging of population, a
213 concomitant increase in the incidence of endometrial cancer can be observed: the probability
214 of developing endometrial cancer at ages 40–59 is 0.77%, rising to 0.87% at ages 60–69 and
215 1.24% at age > 70 years (17). Hence, as women get older, they have a higher risk of
216 developing endometrial cancer. It is interesting to know the National Institute on
217 Aging estimates that in 2050 there will be 150 million people aged at least 65 years,
218 representing 16% of the world population. Women will make up an increasing share of the
219 population. People aged over 85 years (“the oldest old”) represent 8% of the population aged
220 over 65 years and up to 12% in more developed countries (4). The European Union has the
221 highest percentage of people aged over 65 in the world: currently around 20% and forecast to
222 increase to 30% in 2060 (5). In line with aging of the female population, the incidence of
223 endometrial cancer will increase. In this context, it seems useful to better characterise this
224 disease in the specific population of elderly women.

225

226 *A more aggressive cancer*

227

228 Literature data show that endometrial cancer is more aggressive in elderly women,
229 notably in terms of immunohistological profile and stage at which the disease is discovered. A
230 retrospective American study involving 396 patients showed that, compared to younger
231 patients, those aged over 65 years had significantly more of serous and clear cell subtypes
232 (both histological type 2) associated with a poorer prognosis (18) than the endometrioid
233 subtype ($p = 0.004$) and also more histological grade 3 tumours ($p=0.001$). In this study, a

234 stratified analysis by 4 age groups showed that patients aged over 75 years had serous
235 carcinoma more often than patients aged below 45 years (22% vs 5%; $p=0.055$), and more
236 grade 3 tumours too (42% vs 16% $p=0.001$) (19). A more recent study evaluating biological
237 markers of endometrial cancer aggressiveness, such as mutation of the p53 protein and
238 decreased expression of the E-Cadherin protein, using 136 pathology slides, showed that
239 advancing age is directly correlated with tumour stage ($r=0.29$; $p=0.0008$), expression of a
240 mutated p53 protein ($r=0.25$; $p=0.004$) and is inversely correlated with expression of E-
241 Cadherin ($r = -0.28$; $p=0.001$) (20). An American study evaluating survival in a cohort of 243
242 elderly patients with endometrial cancer demonstrated a significantly higher proportion of
243 serous carcinoma in patients aged over 63 years (28% vs 15%; $p=0.002$) (21). In parallel, an
244 Italian study involving a prospective cohort of 108 patients with endometrial cancer and
245 comparing laparoscopy in women over vs below 65 years found significantly more grade 3
246 tumours in the older group (33.3% vs 16.7%; $p=0.05$) (22). In this study, the tumour
247 histological types were similar in both groups. A Canadian study comparing the management
248 of endometrial cancer by robotic surgery in patients aged below 70 years, from 70 to 80 years
249 and over 80 years found that both FIGO (International Federation of Gynecology and
250 Obstetrics) stage and histological grade were more advanced in the older group ($p=0.023$ and
251 $p=0.002$, respectively) (23). In this study, there were no differences between the 3 age groups
252 with regard to histological type 1 (endometrioid carcinoma) or 2. Finally, a similar study by
253 Vaknin *et al.* in 2010 in women aged over versus under 70 years found a higher rate of
254 advanced FIGO stages (III and IV) in the older group (39% vs 18.7%; $p<0.04$) (24).

255 Hence, endometrial cancers affecting elderly women are more aggressive than those in
256 younger patients, in terms of histological type (type 2), histological grade or FIGO stage at the
257 time of diagnosis. The FIGO stage reflects the degree of advancement of the disease and it
258 correlates directly with 5-year survival (25). The observation that disease is more advanced at
259 time of diagnosis in elderly patients may be directly due to the fact that their tumours are
260 inherently more aggressive. Alternatively, it may be due to delays in the management of
261 elderly people or a delay on the part of the elderly person in seeking care, given that 20% of
262 elderly people wait at least one year before consulting for clearly defined symptoms (26).

263

264

265

266

267

268 ***Which carcinogenesis?***

269

270 The difference in histology has been described for several years and it reflects two
271 different pathways of carcinogenesis. The first, the “classic” pathway, starts with a
272 hyperplastic precursor or an atypical hyperplastic component that, following oestrogenic
273 stimulation, undergoes malignant transformation into endometrioid adenocarcinoma. These
274 tumours are more frequent in younger, obese patients and are associated with a less advanced
275 stage and grade. The other “alternative” pathway starts with an atrophic endometrium without
276 oestrogenic stimulation and leads to development of serous cancers of the endometrium. This
277 second type is more frequent in elderly women and is associated with a more advanced stage
278 and grade, and also with poorer prognosis (27). These pathophysiological hypotheses are
279 corroborated by literature data showing that BMI (Body Mass Index) is lower in elderly
280 women with endometrial cancer. Lachance *et al.* divided their 396 patients into 3 age groups
281 (< 45 years, 46–64 years, > 65 years) and found an inverse relationship between age and BMI
282 (40.3, 35.3, 31 respectively; $p < 0.001$) (19). In their retrospective study involving 338 patients
283 with endometrial cancer aged over 50 years, Fleming *et al.* assessed age as a predictor of poor
284 prognosis and similarly found that patients aged 50–69 had a mean BMI of 31 while those
285 aged > 70 had a mean BMI of 28 ($p = 0.004$) (28). The previously mentioned Canadian study
286 in women with endometrial cancer found a mean BMI of 32.8 in patients < 70 years, 30.2 in
287 those aged 70–80 and 21.5 for those aged > 80 ($p = 0.0001$) (23).

288 These morphological data are in favour of a carcinogenesis via the alternative pathway.

289

290 ***Survival and recurrence***

291

292 The prognosis of endometrial cancer is grimmer in elderly patients. An American
293 study from 2003 involving 405 patients with stage IB or II (former FIGO classification)
294 endometrial cancer divided into 2 age groups, older and younger than 70 years, found a higher
295 rate of recurrence in the older group (12% vs 5%; $p = 0.03$) (29). It also found a lower 5-year
296 cancer-specific survival rate in the older group (82% vs 95%; $p = 0.03$). On multivariate
297 analysis, age over 70 years was also a significant factor predictive of poorer survival
298 ($p = 0.03$). Disease-specific survival was also less good in elderly women on both univariate
299 and multivariate analysis ($p = 0.02$ and 0.03 respectively). In their cohort of 243 patients, Jolly
300 *et al.* (2006) found that the 5-year recurrence rate was higher in patients aged over 63 years

301 compared to those aged below 63 years (32% vs 15%; $p=0.02$), and that endometrial cancer-
302 specific survival was worse in the older patients (75% vs 91%; $p=0.003$) (21). In 2013, an
303 Italian study involving 124 elderly patients with endometrial cancer found that disease-
304 specific survival was lower in those aged over 80 years than in those aged below 80 years
305 (56% vs 83%; $p=0.008$) (30). Only Fleming *et al.* did not find a significant difference in
306 recurrence-free survival and disease-specific survival between patients aged over versus
307 below 70 years (28).

308 Compared to younger patients, elderly patients with endometrial cancer have a higher
309 recurrence rate and higher cancer-specific mortality.

310 One question remains unanswered by the literature: is there a difference in survival between
311 the two age groups when histology is similar? If this is the case, is the (surgical and adjuvant)
312 management of this cancer in elderly women not less optimal? (31) (32). In spite of elderly
313 patients want their cancer to be treated as radically and completely as possible (33), this
314 possible undertreatment could be explained by apprehension among medical practitioners
315 about providing onerous treatments to this frailer patient group.

316

317 What surgical management for elderly patients?

318

319 Today, management of endometrial cancer is determined by the FIGO classification,
320 which is based on the histology of the tumour, and lymph node involvement, obtained by
321 lymphadenectomy and histopathological analysis. One question concerning elderly women
322 with endometrial cancer is whether they receive optimal surgical management and by which
323 approach: vaginal, laparotomic, or laparoscopic assisted by robot or not? This then leads to
324 the question about the morbidity of surgical management in patients considered to be frailer.

325 The bibliographic search identified 16 trials looking at the issue of surgical management of
326 endometrial cancer in elderly people. Among these trials, 2 looked at the vaginal approach
327 (30) (34), 2 at the laparotomic approach (19) (35), 8 at the laparoscopic approach (22) (36)
328 (37) (38) (39) (40) (41) (42) and 4 at the robotic approach (23) (24) (43) (44). There were 5
329 retrospective studies (19) (34) (36) (39) (41), 7 prospective studies (22) (23) (24) (30) (35)
330 (38) (44), 2 randomised studies (37) (40) and 2 retrospective surveys using a prospective
331 database (42) (43). The age criterion varied among the studies: it was 63, 65, 70, 75 or 80
332 years. There were also differences from a methodological viewpoint: some of the studies
333 compared two surgical approaches in the management of endometrial cancer in elderly

334 women, while the others compared a single approach in elderly women versus younger
335 women. The studies are summarised in Table 1.

336

337 *Perioperative data*

338

339 The first results collected concern perioperative data. The Susini study comparing the
340 vaginal approach to laparotomy in patients aged over 70 years found a shorter operative time
341 in the vaginal group ($p=0.01$) (34). In their study comparing laparotomy in patients aged over
342 and under 70 years, Vaknin *et al.* did not find a difference in operative time between the age
343 groups (35); neither did Lachance *et al.* in their study (19). Among the studies comparing
344 laparoscopy and laparotomy in elderly women, only the study by Scribner *et al.*, with a cut-
345 off age of 65 years, found a shorter operative time in the laparotomy group ($p=0.0001$) (36).
346 The study by Bogani *et al.* did not find significant difference in operative time between the
347 laparoscopic group and the laparotomic group (42). Studies comparing laparoscopy in elderly
348 women with laparoscopy in younger women did not find significant difference in operative
349 time between the two groups (22, 39, 41). The study comparing laparotomy with robotic
350 surgery found a shorter operative time in the laparotomy group ($p=0.009$) (44). Vaknin *et al.*,
351 looking at management of endometrial cancer by robotic surgery, found a similar operative
352 time in patients aged over and under 70 years (253 min vs 243 min) (24); similar results were
353 found by Lowe *et al.*, who looked at the robotic approach in patients aged over and under 80
354 years (192 min vs 167 min) (43) and by Zeng *et al.* in patients aged <70 years, 70–80 years
355 and >80 years (23). Hence operative time for mini-invasive surgery is not longer in elderly
356 women with endometrial cancer than in younger women. Only Scribner *et al.* found a longer
357 operative time for laparoscopy compared with laparotomy (36) and Lavoué *et al.* for robotic
358 surgery compared with laparotomy (44). This result is not against use of laparoscopy in this
359 indication because the procedure is the same duration regardless of age and the study is quite
360 old (2001). However, it does provide a reminder of the learning curve required by surgeons in
361 order to perform this procedure by laparoscopy in a safe and sufficiently short manner (45).
362 With regard to blood loss and transfusion rate, the study by Susini *et al.* found significantly
363 less blood loss in the vaginal approach group than in the laparotomy group ($p=0.01$), but no
364 significant difference between these two groups in terms of transfusion rate (34). Conversely,
365 Scribner *et al.* found a higher transfusion rate in the laparoscopy group ($p<0.0001$) but no
366 significant difference in blood loss between the laparoscopy group and the laparotomy group

367 (36). The Lachance study comparing laparotomy in different age groups did not find a
368 significant difference in blood loss (19); similarly the Vaknin study did not find a difference
369 in terms of transfusion (35) in women aged over or under 70 years who underwent a
370 laparotomy. The Bogani *et al.* study comparing laparoscopy with laparotomy in women aged
371 over 75 years found significantly less blood loss in the laparoscopy group ($p=0.005$) but no
372 difference between the 2 groups in terms of transfusions (42). However Ghezzi *et al.* report a
373 lower rate of transfusions in the laparoscopy group ($p<0.05$) (38). Studies comparing
374 laparoscopy in elderly women with laparoscopy in younger women did not find any
375 significant differences between these two groups, in terms of either blood loss or transfusion
376 rate (22, 39, 41). Robotic surgery was associated with less blood loss when compared to
377 laparotomy ($p=0.0001$) (44), and there was no significant difference in blood loss between
378 older and younger women (23) (24) (43). Hence, blood loss is equivalent in elderly women
379 and younger women for a given surgical approach, and is higher for laparotomy compared
380 with laparoscopy and robotic surgery (42) (44).

381 Studies comparing outcomes of laparoscopic and robotic modalities in elderly women versus
382 younger women found a similar rate of conversion to laparotomy in both groups (22, 23, 39,
383 40, 41, 43). Only one study, the randomised Gynecologic Oncology Group (GOG)
384 LAP2 Trial, found a higher rate of conversion for more advanced age (OR = 1.27; 95% CI:
385 1.14 to 1.42 per additional decade) (37). According to the literature, laparoscopic or robotic
386 surgery in elderly patients is not associated with a higher rate of conversion to laparotomy.
387 The comparative perioperative data are summarised in Table 2.

388

389 **Complications**

390

391 Other observations concern perioperative and postoperative complications. In this
392 regard, Susini *et al.* did not find a significant difference in the number of severe complications
393 that occurred in patients aged over 70 years who underwent a surgery by the vaginal route or
394 who by laparotomy (19). None of the studies comparing laparoscopy with laparotomy in
395 elderly women found a statistically significant difference in perioperative complications (36,
396 38, 40, 42). However, two studies have shown that there are significantly fewer postoperative
397 complications in the laparoscopy group than in the laparotomy group (15/33, $p=0.002$ (36)
398 and 5/24, $p=0.05$ (42) respectively). The other studies did not find a significant difference
399 between the laparoscopy group and the laparotomy group in terms of perioperative

400 complications (0% versus 5% (38) and 5.3% versus 4.3% (40)) or postoperative
401 complications (6.3% versus 9.5% (38) and 23.7% versus 17.4% (40)).

402 Studies looking at outcomes in elderly versus younger women following laparoscopy did not
403 find any significant differences between the two groups in terms of overall complications
404 (6.4% versus 2.7%) (39), perioperative complications (4.2% versus 1.7%) or postoperative
405 complications (25% versus 23.3%) (22). Similar findings were reported in a study comparing
406 laparotomy outcomes in women aged over versus under 70 years in terms of overall
407 complications (41.7% vs 41.9%) (35), and in a study comparing outcomes following robotic
408 surgery (24). However, De Marzi *et al.*, looking at laparotomy, found a higher rate of
409 perioperative complications in women aged over 75 years (23% vs 9%, $p=0.032$) (30).
410 Interestingly, this significant difference vanishes if a cut-off age of 80 years is used (30). The
411 study by Lowe *et al.* looking at robotic surgery in patients aged over versus under 80 years
412 did not find more perioperative complications in the older women but it did find more
413 postoperative complications in the older group (33% vs 13%; $p=0.022$) (43). Similar findings
414 were reported in another study on robotic surgery that divided patients into 3 age groups: the
415 rate of perioperative complications was similar in the 3 groups (0.5% vs 0% vs 3%), while
416 there was a higher rate of grade III or IV (Clavien Dindo classification (46)) postoperative
417 complications in patients aged over 80 years compared to those aged below 80 years (10% vs
418 1% vs 0%; $p=0.0035$) (23). Lavoué *et al.*, comparing the robotic approach with laparotomy,
419 found significantly more Clavien Dindo grade I/II postoperative complications in the
420 laparotomy group (17% vs 60%; $p<0.0001$) but no difference was found with regard to grade
421 III/IV complications (44). The comparative data concerning perioperative and postoperative
422 complications are summarised in Table 3.

423 For a given surgical approach, elderly patients do not have more perioperative complications
424 than younger patients. However, surgical management of endometrial cancers in this age
425 group by laparotomy is associated with more morbidity than vaginal, laparoscopic or robot-
426 assisted modalities in terms of operative time, blood loss and perioperative complications.

427

428

429 ***Length of hospital stay***

430

431 Susini *et al.* found that the hospital stay was shorter in women operated on vaginally
432 approach (6 days (d) vs 10 d; $p=0.05$ (34)). Studies comparing laparoscopy with laparotomy
433 showed that the hospital stay was significantly shorter for patients who underwent
434 laparoscopy (3 d versus 5.6 d; $p<0.0001$ (36); 2 d versus 6 d; $p<0.05$ (42); 2.5 d versus 7 d;
435 $p<0.05$ (38)). The randomised GOG LAP2 trial (37) found that the proportion of patients
436 requiring more than 2 days of hospitalisation after surgery was significantly lower in the
437 laparoscopy group than in the laparotomy group (52% versus 94%; $p<0.0001$). In the two
438 studies comparing laparotomy in elderly women of different ages, one of them did not find a
439 significant difference in length of hospital stay in women between older vs younger than 70
440 years (35), while De Marzi *et al.* found a longer stay in women aged over 80 years (9.3 d vs
441 7.7 d; $p=0.036$ (30)). Studies comparing laparoscopy with the robotic approach in elderly
442 women of different ages did not find a significant difference between the 2 or 3 age groups in
443 terms of length of hospital stay (22, 23, 24, 39, 40, 43). In a comparison of robotic surgery
444 with laparotomy, length of hospital stay was longer in women aged over 70 years who
445 underwent a laparotomy (3.1 d vs 8 d; $p<0.0001$ (43)).

446 The use of mini-invasive surgery (laparoscopy and robotic) to manage endometrial cancers in
447 elderly women is associated with a shorter hospital stay than laparotomy or the vaginal route;
448 furthermore, the elderly women undergoing mini-invasive surgery are not hospitalized longer
449 than younger women (Table 4).

450

451 Treatment of endometrial cancers is primarily surgical. Historically, surgery was
452 performed by laparotomy, but in the last decade several studies have demonstrated the
453 feasibility and advantages of laparoscopy and robotic surgery in the management of
454 endometrial cancer in all patients (47) (48) and consequently have driven change in surgical
455 practice in favour of laparoscopy and robotic surgery, the optimal surgical modalities with the
456 lowest morbidity in this indication. Nevertheless, when it comes to surgical management of
457 “elderly” patients with endometrial cancer, today’s medico-surgical teams have still not
458 converted to the mini-invasive approach. Yet the present literature review shows that, in spite
459 of the higher burden of comorbidities, elderly patients can also benefit from mini-invasive
460 surgery to manage their endometrial cancer, in terms of blood loss, perioperative
461 complications and length of hospital stay.

462 ***Surgical staging***

463

464 Surgical management of endometrial cancers notably includes pelvic and/or lumbo-
465 aortic nodal staging. Among the previously cited studies, only the studies by Vaknin *et al.*
466 comparing laparotomy or robotic surgery in patients older vs younger than 70 years found that
467 significantly more lymph nodes were removed in patients below 70 years (4 vs 10.4; $p < 0.001$
468 (35) and 10 vs 13; $p = 0.00613$ (24)). Studies comparing the number of lymph nodes removed
469 by laparoscopy or laparotomy in elderly women with endometrial cancer aged over vs under
470 65 years (36) or 75 years (42), or by robotic surgery compared to laparotomy (44) or those
471 comparing the number of lymph nodes removed by laparoscopy in women aged over vs
472 below 65 years (22, 39) or 70 years (41), similarly by laparotomy (19) or by robotic surgery
473 (23, 43) did not find a significant difference in terms of the number of lymph nodes removed
474 as function of patient age (Table 5). According to these studies, mini-invasive surgery appears
475 to be a completely satisfactory technique for performing lymph node staging in endometrial
476 cancers in elderly women.

477 From an oncology viewpoint, it can be seen that there is no significant difference in
478 the number of lymph nodes removed as a function of age for a given surgical approach,
479 except in the two studies by Vaknin *et al.* This could be explained by the fact that the
480 surgeons in these two studies perform less-complete lymphadenectomies when patients are
481 older, even though their disease is more aggressive. This gives rise to an important question
482 not answered by the present literature review: independently of the lymph node number, do
483 surgeons perform lymphadenectomy in elderly patients when this is recommended? It is
484 known that in general oncological surgery, elderly patients are often undertreated (49) so it is
485 pertinent to ask whether this is the case for endometrial cancer. Today, lymphadenectomy in
486 the management of endometrial cancers is recommended or not as function of FIGO stage and
487 tumour histology. Lymphadenectomy extends operative time, itself a morbidity factor in
488 women aged over 80 years, given that a 30-minute increase leads to a 17% increase in the
489 complication rate (50) in this age group. Furthermore, it is associated with perioperative
490 (vascular and neural) and postoperative (lymphoedema and neurological) risks. However, in
491 view of the higher severity of endometrial cancer in elderly patients, it would be legitimate to
492 perform lymphadenectomies more often. Further studies are required in order to determine
493 whether nodal staging is performed or not in this age group and, if it is performed, to
494 determine the associated morbidity, given that this information is not found in the literature.

495 **CONCLUSION**

496 The incidence of endometrial cancer is increasing in line with the aging of the female
497 population. In elderly women, this cancer is more aggressive yet often undertreated. This
498 aggressiveness calls for optimal surgical management by the mini-invasive approach
499 (including a lymphadenectomy when recommended) subject to oncogeriatric evaluation of
500 frailty. Although frailty is better than age at predicting surgical morbidity, it is currently
501 poorly defined — there is therefore a need to develop a short, quick score for predicting
502 surgical morbidity.

503

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ACCEPTED MANUSCRIPT

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- 659
- 660

661 **Table 1:** *Studies looking at management of endometrial cancer in elderly women*

Authors	Year	Study type	Number of patients	Age (years)	Comparison
Scribner <i>et al.</i> ³⁶	2001	Retrospective	125	≥ 65	Laparotomy vs laparoscopy
Susini <i>et al.</i> ³⁴	2004	Retrospective	171	≥ 70	Vaginal vs laparotomy
Lachance <i>et al.</i> ¹⁹	2006	Retrospective	396	≥ 65	Age
Vaknin <i>et al.</i> ³⁵	2009	Prospective	115	≥ 70	Age
Walker <i>et al.</i> ³⁷	2009	Randomized study	1682	≥ 63	Laparotomy vs laparoscopy
Ghezzi <i>et al.</i> ³⁸	2010	Prospective	231	≥ 70	Laparotomy vs laparoscopy
Siesto <i>et al.</i> ²²	2010	Prospective	108	≥ 65	Age
Vaknin <i>et al.</i> ²⁴	2010	Prospective	100	≥ 70	Age
Lowe <i>et al.</i> ⁴³	2010	Retrospective	395	≥ 80	Age
Frey <i>et al.</i> ³⁹	2011	Retrospective	129	≥ 65	Age
Bijen <i>et al.</i> ⁴⁰	2011	Randomized study	238	≥ 70	Laparotomy vs laparoscopy
Perrone <i>et al.</i> ⁴¹	2012	Retrospective	210	≥ 70	Laparotomy vs laparoscopy
De Marzi <i>et al.</i> ³⁰	2013	Prospective	124	≥ 75	Age
Zeng <i>et al.</i> ²³	2013	Prospective	373	≥ 70; ≥ 80	Age
Bogani <i>et al.</i> ⁴²	2014	Retrospective	125	≥ 75	Laparotomy vs laparoscopy
Lavoue <i>et al.</i> ⁴⁴	2014	Prospective	163	≥ 70	Laparotomy vs Robot

663

664 **Table 2:** Perioperative data from studies looking at surgical management of endometrial
 665 cancer in elderly women

Study	Type	Operative time (min)	Blood loss (ml)	Transfusions (%)	Conversion (%)
Susini <i>et al.</i> ³⁴	Vag/Ltm ≥ 70	46/115 p=0.01	210/400 p=0.01	7/5 NS	N/P
Vaknin <i>et al.</i> ³⁵	Ltm ≥ 70/ < 70	141/132 NS	N/P	10/4 NS	N/P
Lachance <i>et al.</i> ¹⁹	Ltm ≥ 65/ < 65	176/185 NS	384/450 NS	N/P	N/P
Scribner <i>et al.</i> ³⁶	Lscp / Ltm ≥ 65	236/148 p=0.0001	298/336 NS	19.2/2.2 p<0.0001	22
Bogani <i>et al.</i> ⁴²	Lscp / Ltm ≥ 75	120/90 NS	100/175 p=0.005	2/6 NS	2
Ghezzi <i>et al.</i> ³⁸	Lscp / Ltm ≥ 70	N/P	N/P	4.2/26.5 p<0.05	N/P
Frey <i>et al.</i> ³⁹	Lscp ≥ 65/ < 65	229/223 NS	165/166 NS	3.2/2.7 NS	0/0
Siesto <i>et al.</i> ²²	Lscp ≥ 65/ < 65	182/175 NS	100/100 NS	4.2/1.7 NS	0/0
Bijen <i>et al.</i> ⁴⁰	Lscp ≥ 70/ < 70	N/P	N/P	N/P	10.5/10.9 NS
Perrone <i>et al.</i> ⁴¹	Lscp ≥ 70/ < 70	267/286 NS	N/P	N/P	2/4 NS
Vaknin <i>et al.</i> ²⁴	Rob ≥ 70/ < 70	243/253 NS	83/81 NS	N/P	N/P
Lowe <i>et al.</i> ⁴³	Rob ≥ 80/ < 80	192/167 NS	50/50 NS	N/P	3.7/7 NS
Zeng <i>et al.</i> ²³	Rob ≥ 80/ 80 to 70/ < 70	237/249/241 NS	88/69/78 NS	N/P	1/1/4 NS
Lavoue <i>et al.</i> ⁴⁴	Rob/Ltm ≥ 70	244.2/217.7 p=0.09	74.8/234 p=0.0001	N/P	N/P

666 Vag: vaginal; Ltm: Laparotomy; Lscp: Laparoscopy; Rob: Robotic; min: minutes; ml:
 667 millilitres; % : percentages; NS: non-significant; N/P: not provided.

668

669

670 **Table 3:** Rate of complications found in studies looking at surgical management of
 671 endometrial cancer in elderly women

Study	Type	Perioperative complications (%)	Postoperative complications (%)	Overall complications
Susini <i>et al.</i> ³⁴	Vag/Ltm ≥ 70	N/P	N/P	5.4/7 NS
Scribner <i>et al.</i> ³⁶	Lscp / Ltm ≥ 65	7/0	15/33 p = 0.002	N/P
Bogani <i>et al.</i> ⁴²	Lscp / Ltm ≥ 75	3/2 NS	5/24 p = 0.05	N/P
Ghezzi <i>et al.</i> ³⁸	Lscp / Ltm ≥ 70	0/5 NS	6.3/9.5 NS	N/P
Bijen <i>et al.</i> ⁴⁰	Lscp / Ltm ≥ 70	5.3/4.3 N/T	23.7/17.4 N/T	28.9/21.7 N/T
Frey <i>et al.</i> ³⁹	Lscp ≥ 65/ ≤ 65	N/P	N/P	6.4/2.7 NS
Siesto <i>et al.</i> ²²	Lscp ≥ 65/ ≤ 65	4.2/1.7 NS	25/23.3 NS	N/P
Vaknin <i>et al.</i> ³⁵	Ltm ≥ 70/ < 70	N/P	N/P	41.7/41.9 NS
DeMarzi <i>et al.</i> ³⁰	Ltm ≥ 75/ < 75	N/P	N/P	23/9 p = 0.032
Vaknin <i>et al.</i> ²⁴	Rob ≥ 70/ < 70	0/2 NS	12/5* NS	N/P
Lowe <i>et al.</i> ⁴³	Rob ≥ 80/ < 80	7.4/5.1 NS	33/13 p = 0.022	N/P
Zeng <i>et al.</i> ²³	Rob ≥ 80/ 80 to 70/< 70	3/0/0.5 NS	10/1/0* p = 0.0035	N/P
Lavoue <i>et al.</i> ⁴⁴	Rob/Ltm ≥ 70	N/P	17/60** p < 0.0001	N/P

672 Vag: vaginal; Ltm: Laparotomy; Lscp: Laparoscopy; Rob: Robotic; NS: non-significant; N/T:
 673 not tested; N/P: not provided; * grade I/II or ** grade III/IV complications of the Clavien
 674 Dindo classification

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678 **Table 4:** Length of hospital stay in studies looking at surgical management of endometrial
 679 cancer in elderly women

Study	Type	Length of hospital stay (d)	p value
Susini <i>et al.</i> ³⁴	Vag/Ltm ≥ 70	6/10	0.05
Scribner <i>et al.</i> ³⁶	Lscp / Ltm ≥ 65	3/5.6	p < 0.0001
Bogani <i>et al.</i> ⁴⁸	Lscp / Ltm ≥ 75	2/6	p < 0.0001
Ghezzi <i>et al.</i> ³⁸	Lscp / Ltm ≥ 70	2.5/7	p < 0.05
Frey <i>et al.</i> ³⁹	Lscp $\geq 65 / \leq 65$	2.9/1.7	NS
Siesto <i>et al.</i> ²²	Lscp $\geq 65 / \leq 65$	2/2	NS
Perrone <i>et al.</i> ⁴¹	Lscp $\geq 70 / < 70$	3.6/3.6	NS
Vaknin <i>et al.</i> ³⁵	Ltm $\geq 70 / < 70$	5.4/4.9	NS
DeMarzi <i>et al.</i> ³⁰	Ltm $\geq 80 / < 80$	9.3/7.7	p = 0.036
Vaknin <i>et al.</i> ²⁴	Rob $\geq 70 / < 70$	2/1	NS
Lowe <i>et al.</i> ⁴³	Rob $\geq 80 / < 80$	1/1	NS
Zeng <i>et al.</i> ²³	Rob $\geq 80 / 80$ to $70 / < 70$	2/1/1	NS
Lavoue <i>et al.</i> ⁴⁴	Rob/Ltm ≥ 70	3.1/8	p < 0.0001

680 Vag: vaginal; Lscp: Laparoscopy; Ltm: Laparotomy; Rob: Robotic; d: days; NS: non-
 681 significant.

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688 **Table 5:** Mean number of lymph nodes removed in studies looking at surgical management of
 689 endometrial cancer in elderly women

Study	Type	No of pelvic lymph nodes	No of lombo-aortic lymph nodes	Total No of lymph nodes	p value
Scribner <i>et al.</i> ³⁶	Lscp / Ltm ≥ 65	17.8/19.1	6.6/5.2	N/P	NS
Bogani <i>et al.</i> ⁴²	Lscp / Ltm ≥ 75	N/P	N/P	14/13	NS
Frey <i>et al.</i> ³⁹	Lscp $\geq 65 / \leq 65$	N/P	N/P	19.2/17.3	NS
Siesto <i>et al.</i> ²²	Lscp $\geq 65 / \leq 65$	N/P	N/P	18/18	NS
Perrone <i>et al.</i> ⁴¹	Lscp $\geq 70 / < 70$	N/P	N/P	15.2/18.6	NS
Vaknin <i>et al.</i> ³⁵	Ltm $\geq 70 / < 70$	N/P	N/P	4/10.4	<0.001
Lachance <i>et al.</i> ¹⁹	Ltm $\geq 65 / < 65$	N/P	N/P	17.9/14.7	NS
Vaknin <i>et al.</i> ²⁴	Rob $\geq 70 / < 70$	N/P	N/P	11/13	0.006
Lowe <i>et al.</i> ⁴³	Rob $\geq 80 / < 80$	N/P	N/P	16/16	NS
Zeng <i>et al.</i> ²³	Rob $\geq 80 / 80$ to $70 / < 70$	N/P	N/P	9.7/10.3/11.8	NS
Lavoue <i>et al.</i> ⁴⁴	Rob /Ltm ≥ 70	8.8/8.4	N/P	10.3/9.7	NS

690 Lscp: Laparoscopy; Ltm: Laparotomy; Rob: Robotic; No: number; NS: non-significant; N/P:
 691 not provided.

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