



Management of endometrial, ovarian and cervical cancer in the elderly: current approach to a challenging condition

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Abstract

Purpose Gynaecological cancer management in older people represents a current challenge. Therefore, in the present paper, we aimed to gather all the evidence reported in the literature concerning gynecological cancers in the elderly, illustrating the state of art and the future perspectives.

Methods We searched MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, IBECs, BIOSIS, Web of Science, SCOPUS and Grey literature (Google Scholar; British Library) from January 1952 to May 2017, using the terms “ovarian cancer”, “endometrial cancer”, “cervical cancer”, “gynecological cancers” combined with ‘elderly’, ‘cancer’, ‘clinical trial’ and ‘geriatric assessment’.

Results The search identified 81 citations, of which 65 were potentially relevant after initial evaluation and met the criteria for inclusion and were analyzed. We divided all included studies into three different issues: “Endometrial cancer”, “Ovarian cancer” and “Cervical cancer”.

Conclusions The present literature review shows that, in spite of the higher burden of comorbidities, elderly patients can also benefit from standard treatment to manage their gynecological cancers. It is important to overcome the common habit of undertreating the elderly patients because they are more fragile and with a lower life expectancy than their younger counterpart. Further trials with elderly women are warranted.

Keywords Gynaecological cancers · Elderly · Ovarian cancer · Cervical cancer · Endometrial cancer

Introduction

Cancer is defined as a disease of older adults. In fact, new cases diagnosis and deaths occurred after age 65 [1]. It has been estimated that since the incidence of cancer has increased 11-fold after age 65 compared to adults up to 65 years, in the coming years it will be registered a considerably increasing in the number of elderly patients with cancer, although the overall incidence of cancer is constantly decreasing [2, 3].

To face this soon-to-erupt phenomenon of elderly patients with cancer an appropriate management is needed, for which guidelines and evidence-based data are still poor, given the

long-lasting under-representation of elderly patients with cancer in cancer trials.

As we know, older adults are affected by a physiological age-related decreases of organ functions, but the condition of elderly patients also involves the risk of developing individual burden of comorbidities, other impairments and social factors, which may influence their potential for undergoing cancer care.

Today, despite the high prevalence of malignancies in older people, administering the optimal treatment to elderly patients affected by cancer is still an open field. Therefore, in the present paper, we aimed to gather all the evidence reported in the literature about gynecological cancers (in particular, endometrial, ovarian and cervical cancer) in the elderly, illustrating the challenge of providing adequate cancer treatment for this subset of patients.

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Materials and methods

Data sources

We searched MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, IBECs, BIOSIS, Web of Science, SCOPUS, and Grey literature (Google Scholar; British Library) from January 1952 to May 2017. We used the terms “ovarian cancer”, “endometrial cancer”, “cervical cancer”, “gynecological cancers” as text words and as appropriate medical subject headings or equivalent subject heading/thesaurus terms. These aforementioned terms were combined with ‘elderly’, ‘cancer’, ‘clinical trial’ and ‘geriatric assessment’. The reference lists of all available primary studies were reviewed to identify additional relevant citations. We considered the following outcomes: overall survival, disease-free survival, surgical complications, hospitalization length, different surgical techniques and chemotherapy toxicity profile and compliance.

Screening of abstracts for eligibility

Original studies, meta-analyses and reviews published were considered. In case of duplicate publications from the same team, the most recent study was included. Case reports were excluded. Two investigators (S.C. and S.L.) independently extract the data from the remaining studies. Disagreements about the inclusion or exclusion of studies were initially solved by consensus and, when this was not possible, they were arbitrarily resolved by a third reviewer (R.A.). Finally,

all the authors scrutinized relevant studies and a decision was made on their inclusion in the review.

Study selection and eligibility criteria

A set of explicit criteria was used for selection of the literature: (1) original articles, (2) clinical trials conducted on human species, (3) adult females more than 65 years old and (4) English language.

Results

The search identified a total of 81 citations, of which 65 were potentially relevant following an initial evaluation. These met the inclusion criteria and were analyzed (Fig. 1). We divided all included studies into three different issues: “Endometrial cancer (EC)”, “Ovarian cancer (OC)” and “Cervical cancer (CC)”.

Endometrial cancer

Endometrial cancer is a disease that occurs more often in elderly women with a mean age at diagnosis of 68 years [4]. Unfortunately, on account of the increase in the average age of population, the incidence of EC is today growing and bilateral salpingo-oophorectomy plus lymph node sampling is proposed as standard management [5–8]. Considering the surgical management of EC in elderly people, we identified 16 trials, focused on different surgical approaches: 2 looked at the vaginal approach [9, 10], 2 at the laparotomic approach [11, 12], 8 at the laparoscopic approach [13–20]

81 POTENTIALLY RELEVANT CITATION IDENTIFIED AND SCREENED FOR RETRIEVAL	
Primary survey: excluded	6 study: treats about other cancer types 4 study: treats benign disease or healthy women
71 POTENTIALLY ELIGIBLE STUDIES RETRIEVED FOR MORE DETAILED EVALUATION	
Secondary survey: excluded	6 study: available only in non-english language
65 ELIGIBLE STUDIES IDENTIFIED	

Fig. 1 Flowchart of study selection process

and 4 at the robotic approach [21–24]. Among these studies, 5 were retrospective [10, 11, 14, 17, 19], 7 prospective [9, 12, 13, 16, 21, 22, 24], 2 randomized [15, 18] and 2 retrospective surveys using a prospective database [20, 23].

De Marzi et al. [9] conducted a study cohort evaluating occurrence of operative and postoperative complications and long-term disease-specific survival in 124 elderly patients affected by endometrioid EC. The women included in the study was of age ≥ 65 years and received a primary surgery treatment (abdominal versus vaginal route), according to personal history (age, body mass index and the presence of comorbidities). The results were examined considering two groups according to age (< 75 years and ≥ 75 years) and also the subgroup of patients older than 80 years. No deaths were recorded during the perioperative period. Percentage of perioperative complications was significantly higher for the older subset. Using a logistic regression model, they found out that women with age ≥ 75 years or chronic lung disease or lymphadenectomy are most likely to have perioperative diseases. Women aged ≥ 80 had a statistically significant shorter long-term disease-specific survival.

Susini et al. [10] elaborated a retrospective study with 171 patients (age ≥ 70 years) affected by EC stages I–III, treated with vaginal or abdominal hysterectomy. The aim of their study was to evaluate the differences between these two routes in order of operative and hospitalization data. On the other hand, the impact of vaginal or abdominal hysterectomy on patients in terms of morbidity, mortality and long-term survival was also examined. The main results showed that patients treated with vaginal hysterectomy had a statistically significant shorter operative time ($p = 0.01$), the same was registered for blood loss ($p < 0.05$) and hospitalization stay length ($p < 0.05$). Moreover, the vaginal route awarded also an overall 10-year disease-specific survival of 80% with respect to the abdominal route whose percentage of survival was of 78% ($p > 0.05$). In line with the discussed results, complications were severe in 5.4% of cases in the vaginal group and in 7.0% of the abdominal cases. Zero perioperative deaths were reported after vaginal approach and 2.3% after abdominal procedure, respectively. Taking into account these results, vaginal approach may represent a valid option for the management of elderly women affected by EC.

Lachance et al. [11] focused their work on the impact of age on surgical results among a cohort of 396 patients affected by EC at different age: < 45 years between 46 and 64 years and > 65 years. No difference was detected in the study groups concerning the operative period in terms of lymph node sampling, operative time, blood loss and complication. On the other hand, in the postoperative period, older patients reported more wound infections ($p = 0.002$), cardiac ($p = 0.001$) and intestinal ($p = 0.025$) problems. Moreover, it is necessary to highlight that, concerning histology, older women (> 65 years) had a higher probability

to be affected by papillary serous type, grade 3 and stage IC if compared with younger ward. Therefore, age should be taken into account in planning EC strategies.

Vaknin et al. [12] performed a study cohort with 115 women undergoing explorative laparotomy because affected by endometrioid EC. Study cohort was divided in two groups: < 70 years and ≥ 70 years. The results demonstrated similar issues during perioperative time among the two groups. No deaths were reported during the perioperative period. However, long-term disease-specific survival was significantly poorer for patients aged ≥ 70 years.

Siesto et al. [13] studied a heterogenic sample of 108 women (48 older and 60 younger) treated with laparoscopy because affected by apparently early-stage EC. The study was performed with and with the intent of comparing clinical outcomes. Data reported similar results for operative time, blood loss, blood transfusions, number of lymph nodes removed and problems during intraoperative and postoperative period. However, taking into consideration the 2- and 5-year disease-free survival rates, there were statistically significant differences for older and younger women (82% versus 96%, $p = 0.003$ and 74% versus 93%, $p = 0.0005$). The same situation occurs when the overall 2- and 5-year survival rates are considered (87% versus 98%, $p = 0.006$ and 83% versus 95%, $p = 0.01$).

Scribner et al. [14] retrospectively analyzed data from 125 patients (age ≥ 65 years) affected by early EC, treated with laparoscopy (group 1), laparotomy (group 2) or transvaginal approach (group 3). As a result, they found that the operative time was significantly longer between group 1 and group 2 (236 vs 148 min, $p = 0.0001$); on the other hand, the numbers of pelvic, common iliac and paraaortic lymph node removed as well as the estimated blood loss (298 vs 336 ml, $p = \text{NS}$) were similar between these groups. Blood transfusion occurred in 19.2% of cases in group 1 and 2.2% of cases of group 2 ($p < 0.0001$). As long as concerned, the postoperative issues in group 1 less fevers (6.0 vs 15.6%, $p = 0.01$), postoperative ileus's (0 vs 15.6%, $p < 0.001$), and wound problems (6.0 vs 26.7%, $p = 0.002$) were detected as well as a shorter hospital stay (3.0 vs 5.8 days, $p < 0.0001$). Similarly, group 3 consisted of patients with a mean age of 77.5 years who underwent transvaginal hysterectomy due concomitant health issues. In this group, operative time was 104.5 min and the average hospital stay was 2.1 days without problems related to treatment during the postoperative period.

Walker et al. [15] in a study of 1682 patients affected by EC reported the advantages of laparoscopy as an alternative to traditional due to less moderate to severe problems during postoperative time (14% versus 21%, respectively; $p < 0.0001$) and lower hospital stay.

Similarly, Ghezzi et al. [16] reported the benefits of laparoscopy for the reduction of adverse events, blood loss and

hospital stay in a cohort of older women (≥ 70 years), 116 underwent laparoscopy and 115 underwent laparotomy. By the contrast, the results concerning operative time, number of lymph nodes removed and complications were similar.

Frey et al. [17] conducted a retrospective study with 129 elderly and younger patients affected by EC undergoing laparoscopy or robotics. The two strategies were similar in terms of estimated blood loss, number of lymph nodes removed, operative time, complications, blood transfusion, and conversion to laparotomy and hospital stay.

Bijen et al. [18] conducted a randomized trial with 283 patients affected by early stage EC and treated with total laparoscopic hysterectomy (TLH) or total abdominal hysterectomy (TAH). Comparing the two groups, older patients were more likely to develop problems similarly in the two groups. Therefore, TLH should be adopted routinely in early stage EC, also in elderly (age > 70 years).

The same thing was demonstrated by Perrone et al. [19] in a retrospective study considering laparoscopy as the first choice in the management of early stage EC even in obese and older women.

Similarly, Bogani et al. [20] supported the adoption of laparoscopy as a first treatment line for elderly affected by EC.

Zeng et al. [21] demonstrated the impact of age on clinical outcomes in EC elderly patients treated with robotic surgery. We note, in fact, that a statistically significant increment of stages and grade 3 complications were proportionally related with aging.

On the other hand, Vaknin et al. [22] reported that there were similar outcomes in terms of mean operative times (252 vs 243 min), mean console times (171 vs 175 min) and mean blood loss (83 vs 81 ml) comparing two groups of patients with EC (elderly and younger) treated with robotic approach. They also reported no statistically significant difference between the two age groups concerning the overall issues during perioperative time, hospital stay and postoperative quality-of-life.

Lowe et al. [23] also analyzed a subset of 27 EC patients aged between 80 and 95 years and treated with robotic-assisted hysterectomy and staging. Comparing their clinical outcomes (intraoperative/postoperative issues, percentage of conversion to laparotomy, blood transfusions) to those of control group, no statistically significant difference was detected, supporting the robotic surgery for EC octogenarians and nonagenarians for safety and feasibility.

Lavoue et al. [24] considered 163 elderly EC patients (≥ 70 years) treated with laparotomy or robotic surgery. Women underwent robotic surgery reported longer mean operating times, fewer minor adverse events according to Dindo classification [25], less blood loss and shorter mean hospital stay, with no difference in 2-years disease-free.

We summarized in Table 1 all the above reported results for a rapid overview.

Even if historically the EC treatment is primarily surgical and performed by laparotomy, literature of the last decade [26, 27] has reported the benefits of laparoscopy and robotic surgery in this field, suggesting an important role of these two surgical routes in the management in older women affected by EC and also in case of lymphadenectomy [28, 29]. Our data highlight feasibility and safety of performing surgery in elderly patients affected by EC, particularly in that patients who underwent mini-invasive surgery, laparoscopy and robotic, which reported a shorter hospital stay than laparotomy or the vaginal approach; with no difference when compared to younger women undergoing this type of surgical procedure.

Nevertheless, today, facing with “elderly” EC patients, the mini-invasive approach is still not the first choice. In fact, the standard EC surgical management notably includes pelvic and/or lumbo-aortic nodal staging.

Concerning the above studies, only Vaknin et al. found that a significantly higher number of lymph nodes were removed in patients < 70 years [12, 22]. The other studies [11, 13, 17, 21–23] comparing lymphadenectomy performed in laparoscopy, robotic or laparotomy in EC elderly women did not report any significant difference. Therefore, mini-invasive surgery in EC elderly women seems a valid option also for lymphadenectomy.

Obviously, the reported data are heterogeneous due to different age criterion adopted by authors (it was 63, 65, 70, 75 or 80 years) and for the methodology, in fact some studies compared different surgical approaches, while others compared a single approach at different ages.

Ovarian cancer

Ovarian cancer (OC) is the seventh most common cancer in women worldwide [30]. Almost 50% of OC is diagnosed in women over the age of 65 [31], but in the near future this ratio is expected to increase in accordance with the ageing population and life-expectancy improvements [32, 33]. In one of the earliest published papers among therapeutic strategies in OC elderly patients, Ries et al. [34], in a cohort of 22,000 patients, identified the age as a factor with a significant determining role on relation to survival, with a 5-year survival rate of 45% for women < 45 years and of 8% for those > 85 . In addition, older women were candidate to single-modality treatments (surgery or chemotherapy or hormonal therapy) while multimodality therapy was preferably administered in younger women [35–39]. The same results were reported by Hightower et al. [40] in 1994.

Older patients, in particular > 80 years, are less likely managed by gynecologic oncologists and rarely with an optimal cytoreduction [40, 41], reporting a higher toxicity

Table 1 Data from studies investigating the management of endometrial cancer in elderly women

References	Study type	N. of PTS	Age	Comparison	Operative time (min)	Blood loss (ml)	Transfusions (%)	Conversion (%)	Perioperative complications	Postoperative complications	Overall complications	Length of postoperative stay (days) and p value	N. Of lombo-aortic LFN	Total n. of LFN	p value of LFN
Scribner et al. [14]	Retrospective	125	≥ 65	LTM vs LPS	236/148 p = 0.0001	298/336 NS	19.2/2.2 p < 0.0001	22	7/0	15/33 p = 0.002	N/P	3/5.6 p < 0.0001	17.8/19.1	6.6/5.2	NS
Susini et al. [10]	Retrospective	171	≥ 70	V vs LTM	46/115 p = 0.01	210/4 p = 0.01	7/5 NS	N/P	N/P	N/P	5.4/7 NS	6/10 0.05	-	-	-
Lachance et al. [11]	Retrospective	396	≥ 65	Age	-	-	-	-	-	-	-	-	NP	17.9/14.7	NS
Vaknin et al. [12]	Prospective	115	≥ 70	Age	141/1327 NS	N/P	10/4 NS	N/P	N/P	N/P	41.7/41.9 NS	5.4/4.9 NS	NP	4/10.4	p < 0.001
Walker et al. [15]	RCT	1682	≥ 63	LTM vs LPS	-	-	-	-	-	-	-	-	-	-	-
Ghezzi et al. [16]	Prospective	231	≥ 70	LTM vs LPS	N/P	N/P	4.2/26.5 p < 0.05	N/P	0/5 NS	6.3/9.5 NS	N/P	2.5/7 p < 0.05	-	-	-
Siesto et al. [13]	Prospective	108	≥ 65	Age	182/175 NS	100/100 NS	4.2/1.7 NS	0/0	4.2/1.7 NS	25/23.3 NS	N/P	2/2 NS	NP	18/18	NS
Vaknin et al. [22]	Prospective	100	≥ 70	Age	243/253 NS	83/81 NS	N/P	N/P	0/2 NS	12/5* NS	N/P	2/1 NS	NP	11/13	0.006
Lowe et al. [23]	Retrospective	395	≥ 80	Age	192/167 NS	50/50 NS	N/P	3.7/7 NS	7.4/5.1 NS	33/13 p = 0.022	N/P	1/1 NS	NP	16/16	NS
Frey et al. [17]	Retrospective	129	≥ 65	Age	229/223 NS	165/166 NS	3.2/2.7 NS	0/0	N/P	N/P	6.4/2.7 NS	2.9/1.7 NS	NP	19.2/17.3	NS
Bijen et al. [18]	RCT	238	≥ 70	LTM vs LPS	N/P	N/P	N/P	10.5/10.9 NS	5.3/4.3 N/T	23.7/17.4 N/T	28.9/21.7 N/T	-	-	-	-
Perrone et al. [19]	Retrospective	210	≥ 70	LTM vs LPS	267/286 NS	N/P	N/P	2/4 NS	-	-	-	3.6/3.6 NS	NP	15.2/18.6	NS
De Marzi et al. [9]	Prospective	124	≥ 75	Age	-	-	-	-	N/P	N/P	23/9 p = 0.032	9.3/7.7 p = 0.036	-	-	-
Zeng et al. [21]	Prospective	373	≥ 70; ≥ 80	Age	237/249/241 NS	88/69/78 NS	N/P	1/1/4 NS	3/0/0.5 NS	10/1/0* p = 0.0035	N/P	2/1/1 NS	NP	9.7/10.3/11.8	NS
Bogani et al. [20]	Retrospective	125	≥ 75	LTM vs LPS	120/90 NS	100/175 p = 0.005	2/6 NS	2	3/2 NS	5/24 p = 0.05	N/P	2/6 p < 0.0001	N/P	14/13	NS
Lavoue et al. [24]	Prospective	163	≥ 70	LTM vs Rob	244.2/217.7 p = 0.09	74.8/234 p = 0.0001	N/P	N/P	N/P	17/60** p < 0.0001	N/P	3.1/8 p < 0.0001	8.8/8.4	NP	10.3/9.7

PTS patients, V vaginal, LPS laparoscopy, LTM laparotomy, Rob robotic, RCT randomized, n. number, min minutes, ml millilitres, % percentages, NS non-significant, N/P not provided, N/T not tested, - not available, LFN lymph nodes

*Grade I/II or **grade III/IV complications of the Clavien Dindo classification

profile. In fact, an SEER-Medicare analysis of women aged > 65 years with stage III or IV ovarian cancer treated with primary surgery reported that those admitted electively ($n=4517$) had a 30-day mortality of 5.6%, in comparison with a 30-day mortality of 20.1% of women admitted in emergency. In addition, without consideration for the admission setting, the 30-day mortality in women aged > 75 years with III–IV stage disease and a comorbidity score of ≥ 1 was estimated as 12.7% [42]. As well as concerned toxicities, one retrospective study involving 85 patients aged > 80 years undergoing cytoreductive surgery showed that 13% died prior to discharge and 20% died within 60 days of surgery. Adjuvant therapy was administered to thirteen percent of patients and 43% completed less than three cycles of therapy [43].

Considering, thus, the reported data about toxicity it seems to be better to prefer neoadjuvant chemotherapy (NACT) and interval cytoreductive surgery as first choice in the treatment of elderly patients.

The above-mentioned data report that elderly patients are candidates to fewer and less aggressive surgeries for OC than younger [44, 45]; nevertheless, the influence of age itself on surgical outcomes has been less investigated.

Several large trials have showed that several oncologic strategies used in younger patients were also tolerated by elderly OC patients with good performance status [46, 47]. Supporting this fact, Cloven et al. [44] demonstrated the possibility to satisfactorily perform debulking surgery in elderly women. The study, in fact, reported that 16/18 OC patients < 80 years underwent primary debulking surgery optimally in 25% of cases. The major postoperative morbidities were reported in 38% of patients and in 75% of cases the intensive care unit was necessary. However, most of patients received adjuvant chemotherapy.

In another recent paper, Bruchim et al. [45] highlighted that NACT is more likely used for OC patients > 70 with respect to primary surgery. However, age did not impact on optimal surgical outcomes.

In a paper of 2013, Trillsch et al. [48] showed in a study group of 275 patients that postoperative 60-day-mortality was 2.1% for elderly (aged > 70 years) and 0.4% for younger ($p < 0.001$). Optimal therapy, consisting of no residual tumor at surgery and platinum-based chemotherapy, was more likely received by younger patients than elderly ($p < 0.001$). The median progression-free-survival (PFS) (12 vs. 20 months, $p = 0.022$) and overall survival (OS) (30 vs. 64 months, $p < 0.001$) were less favourable for elderly, even if in a multivariate analysis, age itself did not result as a prognostic factor for PFS as the Eastern Cooperative Oncology Group (ECOG) performance in elderly patients.

Moreover, concerning chemotherapy, it seems to be any significant difference in toxicity between patients aged < or > 65 years receiving cisplatin-based chemotherapy, as

reported by Chiara et al. [49] but the interruption of schedule occurs more frequently in the elderly group.

In an Italian trial, 82 OC patients > 70 years received carboplatin (230 mg/m² every 28 days) and mitoxantrone, with a good profile of tolerance [50].

In the largest study of chemotherapy in elderly gynecologic oncology patients, treated between 1990 and 2000 in four Italian centres [51], 70% were treated for ovarian cancer and 80% had at least one or more comorbid conditions. Among patients treated with first-line chemotherapy, 96 (64.9%) received a platinum-based regimen with no taxane (group 1), 42 (28.4%) received combined platinum/paclitaxel regimens (group 2), and 10 (6.8%) received a taxane-based regimen with no platinum (group 3). Before the starting of first-line chemotherapy, during its administration and at the completion any significant difference in performance status was observed. Grade 3/4 haematological toxicities were reported in 38.2% of patients and 6.8% of the patients discontinued treatment due to toxicity. No significant association was seen concerning the number of comorbidities and toxicities, confirming previous reports [47, 51–54] that the elderly with optimal renal and hepatic functions can well tolerate chemotherapy regimens.

Recently, Fourcadier et al. [55] showed that, without considering the type of treatments, elderly OC women tend to receive less treatment than their younger counterparts. This impact of age was not related to other variables, such as stage and grade. It was also reported that the probability of receiving standard treatment, in accordance with recommendations, was reduced by 50% in elderly patients compared to their younger counterparts. We summarized all the above reported data in Table 2 for a rapid overview.

Cervical cancer

The number of elderly patients affected by cervical cancer (CC) is increasing in Europe, accounting for more than 40% of the deaths from cervical cancer annually [56].

Most of elderly women with CC received different type of treatments compared to their younger counterparts, as literature suggests [57–59]. This is in line with the facts that for all types of cancer the purpose of cure declined with increasing age and that elderly patients were more likely to forego treatment [60]. Sharma et al. [61] reported that, in comparison with younger patients, women > 70 years with early stage tumors were less likely to receive any type of treatment including primary surgery, adjuvant therapy for high-risk features and high-quality radiotherapy.

Early CC stages (stage IB–IIA) are treated with radical hysterectomy or primary radiotherapy; reporting similar survival rate [62, 63]. In the United States, more than 80% of women affected by CC are treated surgically [64], but, if we take into account only elderly women, the percentage of

Table 2 Data from studies investigating the management of ovarian cancer in elderly women

References	Study type	N. of PTS	Age	Survival rate	Surgery	Complications	Postoperative stay	Adjuvant chemotherapy	Chemotherapy toxicities
Ries [34]	Retrospective	22,000	–	< 45 years 45% > 85 years 8% (5-year)	40% > 85 years did not receive any definitive treatment	–	–	–	–
Hightower et al. [40]	Retrospective	12,316	< 80 years > 80 years	Stage I, 89% versus 79%; stage II, 58% versus 40%; stage III, 25% versus 11%; and stage IV, 13% versus 3%	Optimal tumor debulking rates of women greater than or equal to 80 years were significantly less than those of younger patients ($p < 0.001$) The most elderly women were least likely to undergo such surgery [odds ratio (OR), 0.16; 95% confidence interval (CI), 0.13–0.20]	No significant increase in anesthesias complications between age groups	–	Older patients are less likely to receive adjuvant chemotherapy than younger patients (42% versus 69%, $p < 0.0001$) The most elderly women were least likely to receive chemotherapy	–
Fairfield et al. [41]	Retrospective	4589	> 65 years	–	–	–	–	–	–
Thrall et al. [42]	Retrospective	5475	> 65 years	–	–	Overall 30-day mortality was 8.2%	–	–	–
Moore et al. [43]	Retrospective	85	> 80 years	2-Year overall survival for those who underwent CRS followed by adjuvant therapy is 51%	74% underwent suboptimal cytoreduction	15% of patients suffering cardiac or pulmonary complications, over 10% with prolonged ileus, wound complications or mental status changes and over 30% requiring transfusion or antibiotics	–	13% were unable to receive indicated adjuvant therapy	–

Table 2 (continued)

References	Study type	N. of PTS	Age	Survival rate	Surgery	Complications	Postoperative stay	Adjuvant chemotherapy	Chemotherapy toxicities
Cloven et al. [44]	Retrospective	18	> 80 years	Overall median survival was 6 months. In patients with optimal debulking was 32.5 months compared to 3.5 months in patients suboptimally debulked	88% underwent primary debulking surgery	75% blood transfusions of 2 or more units 38% experienced major postoperative morbidity	8 days	83% received chemotherapy	–
Bruchim et al. [45]	Retrospective	143	< 70 years $n = 97$, ≥ 70 years $n = 46$		Elderly group had fewer primary debulking surgical interventions (54.3%) than the younger group [84.5% ($p = 0.001$)]	–	–	92% of the younger patients entered a first-line chemotherapy regimen compared to 65.2% of the older patients ($p = 0.001$). The elderly patients were more likely to receive neoadjuvant chemotherapy (43.3.3% vs 13.4%, $p < 0.01$)	In elderly hematological toxicity was significantly more common (75% vs 36.3%; $p = 0.001$), although no significant difference was noted between the groups in grade 3–4 patients (≥ 70 years, 62.5% vs < 70 years, 45.5%; $p = 0.2$). Elderly were more likely to have dose reductions and treatment delays compared to the younger patients (60% vs 22.4%; $p < 0.001$, and 46.6% vs 19.1%; $p = 0.004$, respectively)

Table 2 (continued)

References	Study type	N. of PTS	Age	Survival rate	Surgery	Complications	Postoperative stay	Adjuvant chemotherapy	Chemotherapy toxicities
Edmonson et al. [47]	Retrospective	383	107 (28%) were 65 years of age or older	–	–	–	–	The elderly women tolerated the five different chemotherapy regimens nearly as well as did the younger patients	Progressively greater dose reductions were required for treatment continuation with advancing age between groups aged 44 years or younger, 45–64 years, and 65 years and older
Trillsch et al. [48]	Retrospective	2750	< 70 years > 70 years	–	Elderly patients were less likely to receive optimal therapy (no residual disease after surgery and platinum combination chemotherapy) compared to patients < 70 years (40.4% vs. 70.1%, $p < 0.001$)	Postoperative 60-day-mortality rate was 2.1% for elderly and 0.4% for younger patients ($p < 0.001$)	–	–	–
Chiara et al. [49]	Randomized	547	< 65 years of age > 65 years	No difference was observed in survival and progression-free survival between younger and older patients	–	–	–	–	No significant difference in toxicity was evident between patients older than and younger than 65 years
Nicoletto et al. [50]	Prospective	82	> 70 years	–	–	–	–	–	Four cases of thrombocytopenia and one case of gastrointestinal toxicity. These 5 episodes occurred in 328 assessable cycles, representing a low toxicity profile (3%)

Table 2 (continued)

References	Study type	N. of PTS	Age	Survival rate	Surgery	Complications	Postoperative stay	Adjuvant chemotherapy	Chemotherapy toxicities
Ceccaroni et al. [51]	Retrospective	148	> 70 years	-	-	-	-	-	G3–G4 hematological toxicity was documented in 38.2% of cases. Only 10 (6.8%) of the 148 patients discontinued treatment because of G3–G4 hematological toxicity. No severe nonhematological toxicity was observed

patients surgically managed decrease at 55% for women aged 70–79 years, and at 33% for those aged > 80 years, against the 82% of women aged < 50 years old. In addition, also when elderly women underwent surgery, radical hysterectomy, considered as standard of care, was rarely performed [61]; nevertheless, the literature reported that radical hysterectomy and regional lymphadenectomy are well tolerated by elderly women [64–68]. Obviously, future population-based studies are advocated to understand the implications of radical hysterectomy in the elderly in terms of morbidity.

Moreover, elderly women were also less likely to receive adjuvant radiotherapy. In fact, among lymph node positive women with early stage tumors treated with primary surgery, more than 90% of them aged > 80 years were less likely to receive radiation than younger counterparts. For advanced CC stages, radiation plus chemotherapy is considered as the best choice of treatment [69–72]. Data of the literature reported that the uptake of chemotherapy has rapidly increased from 34% in 1997 to 85% in 2001 [64]. Radiation remains crucial for advanced CC stages, delivered with external beam radiation (both whole pelvic and parametrial boost) in combination with intracavitary brachytherapy to obtain the optimal local control of the disease [73]. Also in this last case, Sharma et al. unfortunately [61] reported that among elderly patients, fewer than 50% of the women > 80 years of age and only 59% of those aged 70–79 years received brachytherapy. However, prior studies have reported disparities in access to brachytherapy; Mitchell and coworkers [74] noted that 11% of patients 60–69 years old, 20% aged 70–79 years, and 40% of those > 80 years of age did not receive intracavitary radiation.

Recently, several studies have reported that elderly tolerate well pelvic radiotherapy and brachytherapy [73, 75–79]. This fact is confirmed by the European Organization for Research and Treatment of Cancer that found no age-related differences in either early or late toxicities in patients treated with pelvic radiation [78]. Moreover, it was also demonstrated that radiotherapy was well tolerated even in patients aged > 80 years [79]. Grant and colleagues [80] showed that 32% of women aged > 75 years treated with pelvic radiotherapy did not complete therapy and treatment interruptions occurred in 42% of patients. Chemoradiation is well tolerated in elderly even if the long-term outcomes of this option must be investigated [75].

To offer readers a rapid overview, we reported all the data in Table 3.

Discussion

In the next future, an increasing number of elderly patients with cancer is expected. Recognizing this fact as an important and crucial feature is the first step in order to build the

Table 3 Data from studies investigating the management of cervical cancer in elderly women

Authors, year	Study type	N. of PTS	Age	Survival rate	Treatment	Complications	Postoperative stay	Adjuvant chemo-therapy	Chemo-therapy toxicities
Sharma et al. [61]	Retrospective	28.902	All	–	For women with IB1–IIA CC, primary surgery was performed in 82.0% of women <50 years old compared with 54.5% of those 70–79 years old and 33.2% of those ≥80 years old ($p < 0.0001$). For women treated surgically, lymphadenectomy was performed in 66.8% of women <50 years old versus 9.1% of patients ≥80 years old ($p < 0.0001$). Compared with patients <50 years old, those >80 years old were less likely to undergo radical hysterectomy [odds ratio (OR), 0.10; 95% confidence interval (CI), 0.07–0.14] and lymphadenectomy (OR 0.11; 95% CI 0.08–0.16) and to receive adjuvant radiation therapy (OR, 0.06; 95% CI, 0.01–0.35)	–	–	–	–

Table 3 (continued)

Authors, year	Study type	N. of PTS	Age	Survival rate	Treatment	Complications	Postoperative stay	Adjuvant chemo-therapy	Chemo-therapy toxicities
Fuchtmr et al. [65]	Retrospective	135	> 65 years	–	All patients underwent to radical hysterectomy	Transfusions of greater than 2 units were required in 14% of the elderly and 35% of younger patients ($p=0.02$)	–	–	–
Geisler and Geisler [66]	Retrospective	69	> 65 years	–	All patients underwent to radical hysterectomy	Minor morbidity occurred in 14.5% of the group, while major morbidity occurred in 10%. There was no mortality	65 < age < 74 8.7 days > 75 years – 10.4 days	–	–
Levrant et al. [68]	Prospective	123	14 pts > 65 years	No decrease in survival.	All patients underwent radical hysterectomy with pelvic lymphadenectomy and para-aortic node sampling	Minimally increased morbidity in the elderly patient with no increase in long-term complications or	–	–	–
Magné et al. [73]	Retrospective	113	Over 70-year-old	88.6%	All treated by conventional low dose rate (LDR) BT as a part of their treatment	No statistically significant difference	–	–	–
Mitchell et al. [74]	Prospective	398	Ages (35–69) ($n=338$) and elderly (ages ≥ 70)	Equivalent	All patients treated with radiation therapy	–	–	–	–
Goodheart et al. [75]	Retrospective	364	Elderly (≥ 65) and nonelderly (< 65)	Equivalent	Patients treated with definitive radiation therapy	Equivalent	–	–	Equivalent
Ikushima et al. [76]	Retrospective	727	≤ 64 years (younger group, 337 patients), 65–74 years (young-old group, 258 patients), and ≥ 75 years (older group, 132 patients)	The 5-/10-year disease-specific survival rates were 60%/52%, 76%/68% and 66%/57% in the 3 groups	Patients treated with radical radiation therapy	Late radiation morbidity of grades 2–4 in the bladder and/or rectum occurred in 22, 31 and 8% of 3 groups	–	–	–

Table 3 (continued)

Authors, year	Study type	N. of PTS	Age	Survival rate	Treatment	Complications	Postoperative stay	Adjuvant chemo-therapy	Chemo-therapy toxicities
Minagawa et al. [77]	Retrospective	102	All	Five-year survival rates between the two groups, which we have divided for every 5 years of age, showed no differences	Patients treated radical radiation therapy	–	–	–	–
Grant et al. [80]	Retrospective	31	Aged 75 years or older	–	Patients received pelvic radiation therapy	Treatment-related complications were independent of increasing age	–	–	–

necessary collaborations and to apply the optimal treatment strategies in response to this complex phenomenon [81–87].

Elderly patients with cancer should be treated according to their physical health and their preferences. The initial geriatric assessment represents, thus, the starting point to plan the individual best-suited therapy.

However, the present literature review shows that, in spite of the higher burden of comorbidities, elderly patients can also benefit from standard treatments in managing their gynecological cancers.

In this prospective, it is absolutely necessary to overcome the mental bias of not treating the elderly because they are more fragile and have a lower life expectancy than their younger counterparts.

Elderly patients affected by gynecological cancer should benefit of an individualized treatment. Data, in fact, do not support the premise that age itself is a negative prognostic factor, moreover with the objectivity that elderly patients are able to tolerate the standard of care for gynecological cancers.

As functional status does not demonstrate a reliable correlation with either tumor stage or comorbidity, each patient's comorbidities should be assessed independently. For elderly patients with significant medical comorbidity, the extent of surgery and the aggressiveness of chemotherapy should be tailored to the individual's extent of disease, symptoms, overall health, and life goals.

Unfortunately, few clinical trials are specifically designed for older patients and a limited number of elderly patients referred to ongoing trials. A concerted effort should be made to enter older persons into treatment protocols. In addition, enhanced cooperation between geriatricians and oncologists may aid the pretreatment assessment of elderly patients and improve treatment guidelines in this population.

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