World Cancer Research Journal WCRJ 2014; 1 (1): e55

POSTOPERATIVE RADIOTHERAPY AND COMORBIDITY ASSESSMENT IN OLDER AND OLDEST ELDERLY ENDOMETRIAL CANCER PATIENTS: A RETROSPECTIVE ANALYSIS

F. FIORICA, G. ZINI , F. CARTEI, M.V. CANDELA, G. PASCALE, M. BERRETTA[1], A. LLESHI[1], M.R. FALCO ABRAMO[2], L. DEL PUP[3], R. FISICHELLA[4], D. SPARTÀ[4], S. BERRETTA[4], G. FACCHINI[5], S. PRINCIVALLE, A. STEFANELLI

Department of Radiation Oncology, Universitary Hospital "S. Anna" Ferrara, Italy.
[1]Department of Medical Oncology, National Cancer Institute, Aviano, Italy.
[2]Department of Obstetrics and Gynecology, ASP AG1, Agrigento, Italy.
[3]Department of Surgery, National Cancer Institute, Aviano, Italy
[4]Department of Surgery University of Catania, Catania Italy.
[5]Uro-Gynecologic Oncology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione Giovanni Pascale", IRCCS, Napoli, Italia.

ABSTRACT: *The purpose of this study was to evaluate the impact of adjuvant radiotherapy, in terms of feasibility and activity, in women aged ≥ 75 years with endometrial cancer. From January 2000 to December 2009, 53 consecutive patients aged 75 years or older received an adjuvant treatment program after hysterectomy and bilateral salpingo-oophprectomy. Forty-three out of 53 patients received external radiotherapy and vaginal cuff brachytherapy. In 10 women, vaginal cuff brachytherapy alone was delivered. Ten out of 53 received chemotherapy. Variables considered were age, depth of myometrial infiltration and FIGO grade, co-morbidity, performance status, RT dose, brachytherapy and chemotherapy. The mean age was 78.3 years (range 75-88 years). A total of 11.3% of the patients had no co-morbidity, 58.6% mild, 28.3% moderate, and 1.9% had severe co-morbidities. All patients completed the planned radiation schedule. At a median follow-up of 53 months, the 5-year overall survival rate was 72.3%. There was a better survival for patients with no or mild co-morbidities ($p < 0.0001$). No difference in acute and late toxicity rates was found between patients with different ACE-27 (Adult Comorbidity Evaluation-27) indexes and for different age. We conclude that compliance with adjuvant radiotherapy is good and rate of toxicity is acceptable in elderly patients. Patients with no or mild co-morbidities have a significantly better survival. Increasing severity of co-morbidity may sufficiently shorten remaining life expectancy to cancel gains with adjuvant radiotherapy. Further prospective trials are needed to confirm these results.*

Keywords: *Elderly patients, Endometrial cancer, Adjuvant radiotherapy, Co-morbidities.*

INTRODUCTION

Endometrial cancer (EC) is a disease typical of the elderly, incidence data have shown that median age at diagnosis is 62 years and 41.1% of patients were diagnosed over 65 years[1]. This age-associated increase in incidence of EC, together with the expected rise in the number of elderly people, will lead to a higher absolute number of elderly patients with EC.

Furthermore, elderly women with EC have often a poor prognosis, this is thought to be related to more aggressive histologies and less aggressive use of treatment[2,3]. In addition to the prognostic signif-

Corresponding Author: Francesco Fiorica, MD, Ph.D; e-mail: francesco.fiorica@unife.it

icance of age, a number of studies have suggested that elderly women with EC receive less aggressive treatment than their younger counterparts[4,5].

As reported by randomized clinical trials, hysterectomy plus radiotherapy (pelvic radiotherapy and vaginal cuff brachytherapy) is the standard treatment when a deep invasion of the myometrial or grade 3 tumor is present, especially in women under 60 years[6]. Postoperative irradiation is a safe and well-tolerated treatment that can achieve a good local control in high risk endometrial carcinoma.

Despite the importance of age in influencing outcome for EC, the management of elderly patients appears controversial and some more the management of older (age ranged 75-84) and the oldest[7] women (> 85). Moreover, elderly patients are an extremely heterogeneous population as regards co-morbidity. Subjects can vary from very fit to not being able to live independently due to co-morbidities. It is not so clear whether the toxicity of treatment is justified by the level gained as measured by life prolongation and whether co-morbidities can influence the acute and late toxicities due to an active treatment. Nevertheless, female patients who have reached their 80th year still have a mean life expectancy of nine years[8].

In order to clarify this issue, we decided to analyze retrospectively, whether older and oldest cancer patients could benefit from an adjuvant radiotherapy regimen routinely used in younger patients.

PATIENTS AND METHODS

Patient characteristics

The data were collected from 53 patients aged over 75 years that received postoperative radiotherapy in our radiotherapy department for endometrial cancer re-staged to be FIGO (Féderation Internationale de Gynécologie et d'Obstétrique) Stage IA, IB or II[9], between January 2000 and December 2009. In all woman, the clinical workup included a detailed medical history, physical examination, routine blood work, chest X-ray and CT abdomen/pelvis. Pelvis MRI was performed at the discretion of the treating gynecologic or radiation oncologist.

Patient characteristics are summarized in Table 1. The analyzed patients had a performance status ≥60 and a life expectancy of longer than 3 months. The ACE-27 was retrospectively used to take into account co-morbidities[10-12]. The co-morbidity scores were assigned without having any information regarding the outcome of the patient. In the presence of more than one co-morbidity related to an organ system the one with the highest severity was counted. The patients were divided in four subgroups: "no", "mild", "moderate" and "severe" co-morbidities. Furthermore, the patients were grouped in three age groups: 75-80, 80-85 and > 85 years of age.

All women underwent surgical staging and treatment with total abdominal hysterectomy, bilateral salpingo-oophorectomy and peritoneal cytology analysis according to institutional policy. This study has been approved by local ethical committee.

Adjuvant treatment

Forty-three patients had a conformal whole pelvis radiotherapy with 6-15 MV photon beams using CT-assisted three-dimensional treatment planning (Pinnacle™) and vaginal cuff brachytherapy. External radiotherapy was delivered when deep invasion of the myometrial muscle (50% of the depth) or grade 3 tumor with myometrial invasion is present. The median pelvic dose was 45Gy in1.8-Gy daily fractions, dose was prescribed according to the ICRU 50 (International Commission on Radiation Units & Measurements,1993) guidelines. In these patients, a boost with brachytherapy was delivered in two or three fractions of 5-7 Gy. Instead, vaginal cuff brachytherapy alone was delivered in 4 women staged IA G3 and 6 IBG2, in these patients a dose of 21 Gy was delivered in 3 fractions. For the brachytherapy treatments, MicroSelectron high-dose-rate (HDR) machines with an iridium source (Ir-192) was used. Plastic vaginal cylinders with diameters of 20, 25, or 30 mm were used as standards. The diameter of the cylinder was individually chosen to ensure good contact between the surface of the applicator and the vaginal mucosa. Only 10 (9.4%) women received chemotherapy with carboplatin-based schedule because they had an uterine papillary serous carcinoma. All treatments were given on an outpatient basis. During the treatment, patients were monitored for radiotherapy-related toxicities. Acute morbidity was classified according to WHO criteria[13] and recorded weekly during radiation. In endometrial cancer treatments the most common acute side effects are gastrointestinal (diarrhea graded from 0 to 4), genitourinary (urinary frequency/urgency graded from 0 to 3) and cutaneous complications (graded from 0 to 4).

Follow-up and restaging

According to our policy, we evaluate EC patients at 3-month intervals for 2 years and every 6 months thereafter for a total of 5 years. All analyzed study patients received at least two follow-up visits. Evaluations consisted of physical and pelvic examination, complete blood cell counts and blood chemistry exams including CEA and Ca125 level at every follow-up visit, PAP smears and abdomi-

TABLE 1. CHARACTERISTICS OF THE PATIENTS STUDIED.

Parameters		No. of patients (%)	
Age (years)	Range	75-92	
	Mean	79.8	
Age-groups	75-79	28	(52.8)
	80-84	10	(18.9)
	>84 y	15	(28.3)
ACE-27 overall comorbidity score			
	Grade 0	6	(11.3)
	Grade 1	31	(58.5)
	Grade 2	15	(28.3)
	Grade 3	1	(1.9)
Performance status			
	90-100	14	(26.4)
	70-80	32	(60.4)
	60	7	(13.2)
Stages			
	IA	4	(7.5)
	IB	26	(49.1)
	II	23	(43.4)
Grading			
	G1	7	(13.2)
	G2	26	(49.1)
	G3	20	(37.7)
External beam Radiotherapy (EBRT) dose			
	≤ 45	12	(22.6)
	> 45	36	(67.9)
	No EBRT	5	(9.4)
Brachitherapy			
	with EBRT	43	(81.1)
	without EBRT	10	(18.9)
Chemotherapy			
	Yes	10	(18.9)
	No	43	(81.1)

nal/pelvis CT after six months from radiotherapy and then annually. Local relapse was defined as relapse in the pelvis. Distant metastasis was defined as failure beyond the local area. Furthermore, during follow-up examinations, late effects were recorded according to NCI-EORTC criteria[14].

Statistical analysis

The primary endpoint of the study was overall survival. The secondary end-points were: (a) acute and late toxicity rate, (b) disease-free survival and (c) local recurrence and metastases during follow-up. The Kaplan-Meier method[15] was used to estimate survival, late toxicity rate, local recurrence and metastases. Differences in the survival and late toxicity rate were assessed by the log-rank test. The observed survival time was the interval between diagnosis and death or the final follow-up. For overall recurrence, the tumor-free time was the interval between no evidence of neoplastic disease 1-month after treatment and the appearance of the tumor. In this analysis, the follow-up of patients dying without recurrence was censored at the time of death, and these patients were classified as disease-free. An actuarial method was employed to estimate the occurrence of late side effects in relation to time; the late side effect free time was the interval between no evidence of late side effects three months after the radiotherapy. The Cox model[16] was used to identify the risk factors for overall survival, cancer-free survival, and occurrence of late complications.

The following variables at baseline, considered for survival univariate analysis, were: age, depth of myometrial infiltration and FIGO grade, co-morbidity, performance status, RT dose, brachytherapy and chemotherapy. We also considered the rate of acute side effects analyzing the late effects. All analyses were conducted with SPSS vers.13.0 (SPSS for Windows, Rel. 13.0 2004. SPSS Inc., Chicago, IL, USA).

RESULTS

Features of patients at baseline

All patients were eligible for the analysis. Fifteen out of 53 women (28.3%) were over 84 years old, 10 (18.9%) ranged between 80-84 years and 28 (52.8%) between 75-79 years. Patient and treatment characteristics are shown in Table 1. In this cohort, stage IB in 49.1% and stage II in 43.2%, respectively, whereas stage IA was observed in 7.5% of women. In 47 (88.7%) patients at least one co-morbidity was observed (Table 2). The patients' classification of co-morbidities according to ACE-27 index was 0 in 6 (11.3%) patients, 1 in 31 (58.6%), 2 in 15 (28.3%), and 3 in 1 (1.9%) patients, respectively. The Karnofsky performance score was: 60, 70-80 and > 90 in 7 (13.2%), 32 (60.4%) and 14 (26.4%) patients, respectively. Forty-three patients received an adjuvant radiotherapy with a 45 Gy dose with conventional fractionation (1.8 Gy die/ 5 days/week) and brachytherapy boost (10-12 Gy in 2 fractions). Ten patients (9.4%) received only vaginal brachytherapy. Ten out of 53 received chemotherapy. All patients completed the planned treatment.

Follow-up

The median follow-up was 53 months, with a range of 12-120 months. At the time of statistical analysis, 17 patients (32.1%) were dead, 6 of whom (11.3%) due to cancer relapse. Globally, the actuarial overall survival rate at 60 months was 72.3% (Figure 1a). Survival was longer among patients with no or mild co-morbidities (89% at 60 months) than among those with moderate or severe co-morbidities (31.3% at 60 months; $p < 0.0001$ by log-rank test) (Figure 1b). The results of the univariate analysis are shown in Table 3. The multivariate Cox model included age, ACE-27 index, depth of myometrial infiltration, and FIGO grade, stage, PS, RT dose, brachytherapy and chemotherapy for all models. For overall survival, the final multivariable Cox model maintained an ACE-27 index value equal or higher than 2 (HR 6.585; 95% CI = 2.216-19.567, $p < 0.001$).

TABLE 2. DISTRIBUTION OF TYPE AND SEVERITY OF CO-MORBIDITIES.

Co-morbidity	%	ACE-27 grades		
		1	2	3
Total number = 53				
Alcohol abuse	0 –	–	–	
Hypertension	39.6	18	3	0
Respiratory disease	9.4	4	1	0
Congestive heart failure	15.1	6	2	0
Diabetes mellitus	30.2	14	2	0
Arrhythmia	3.8	1	1	0
Myocardial infarction	5.7	2	1	0
Coronary artery disease/angina	9.4	3	2	0
Stroke	1.9	1	0	0
Peripheral arterial disease	1.9	0	1	0
Renal insufficiency	5.7	2	1	0
Gastrointestinal disease	5.7	2	1	0
Dementia	1.9	1	0	0
Psychiatric	1.9	1	0	0
Liver disease	5.7	2	1	0
Paralysis	1.9	1	0	0
Neuromuscular disease	0	–	–	–
Other solid tumor	3.8	1	0	1
Obesity	5.7	2	1	0
Venous disease	5.7	3	0	0
Pancreatic disease	0 –	–	–	
Rheumatological	0 –	–	–	
Inmunological disease/AIDS	0 –	–	–	
Leukemia/myeloma	0 –	–	–	
Lymphoma	0 –	–	–	
Illecit drugs	0 –	–	–	

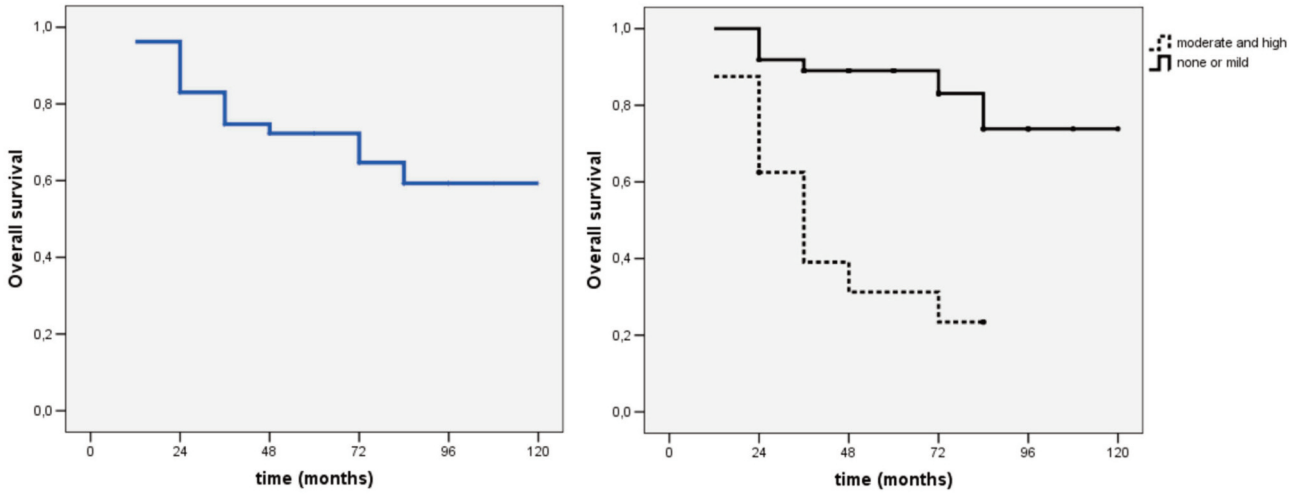

Figure 1. Overall survival curve for all 53 women evaluated *(A)* and in figure *(B)* overall survival distribution by ACE-27 value.

Twelve patients (22.6%) experienced macroscopic tumor recurrence. The distribution of recurrence was as follows: 9 (17%) local recurrences and 3 (5.7%) systemic recurrences. The actuarial local recurrences free survival rate at 5-years was 82.7% (Figure 2a), while the actuarial metastases free survival rate was 96.1% at 5-years (Figure 2b). The actuarial disease-free survival at 60 months was 90%.

Treatment safety

Acute toxicity

The main toxicity was diarrhea that occurred in 39 patients (73.6%): 31 (58.5%) had grade 1 and 8 patients (15.1%) experienced grade 2 diarrhea. Urinary and skin were the second most toxicities, but without grade 3 cases. None of the baseline variables analyzed was significantly associated with the occurrence of acute toxicity.

Late toxicity

Ten patients (18.9%) developed a late toxicity given the variable risk of developing a late effect; an actuarial method was employed to estimate the occurrence of late side-effects in relation to time. The most frequent late toxicity was rectal G1 in 16.9% of subjects. The late side-effects-free survivals were 78.7% at 60 months (Figure 3). No significant differences were found among the three age-groups. There was no relationship between acute toxicity rate and development of late toxicity ($p = 0.815$).

TABLE 3. UNIVARIATE ANALYSIS OF SURVIVAL DATA ACCORDING TO VARIOUS CLASSIFICATIONS

Parameters	Groups	β	± SE	*p* =	HR (95% CI)
Age category	0: 75-79 1: 80-84 2: >84	0.378	0.281	0.179	1.459 (0.841-2.533)
Comorbidity	0: none 1: mild 2: moderate 3: severe	1.885	0.556	< 0.001	6.585 (2.216-19.567)
Stage	0: IA 1: IB 2: II	0.556	0.464	0.231	1.743 (0.702-4.328)
Grading	0: G1 1: G2 2: G3	0.419	0.418	0.316	1.520 (0.670-3.450)
External Beam RT dose	0: ≤45 1: >45 2: no EBRT	0.146	0.518	0.778	1.157 (0.419-3.197)
CT	0: yes 1: no	0.308	0.844	0.715	1.361 (0.260-7.125)

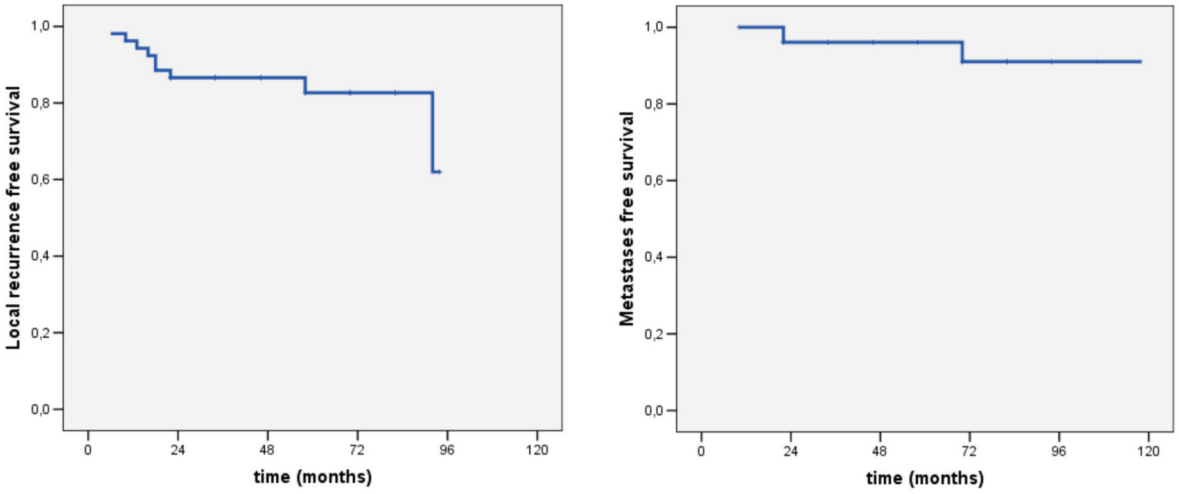

Figure 2. Local recurrences *(A)* and metastases *(B)* free survival for all 53 patients evaluated.

DISCUSSION

Endometrial cancer carry out a poor prognosis in elderly women, an increased rate of aggressive tumor histology, increased tumor grade, and deep myometrial invasion is demonstrated[3,17]. Large, unselected endometrial cancer databases[4,5] show that survival decreased incrementally with advancing age. Therefore, chronological age has been proposed as a independent risk factor[18].

Nevertheless, it is not so clear if the poor prognosis is related to tumor characteristics or to a diagnosis in advanced stage disease or to substandard treatments.

In fact, for many years, it was thought that elderly patients were less tolerant to cancer treatment than younger patients. Surgery plus postoperative radiotherapy is recommended as the standard of care for women with high risk EC. However, a substandard approach is delivered to elderly women. Ahmed et al[4] found that surgery for early EC was performed less often with increasing age, from 90% in patient's age 75-84 years to 76% in age 75-95 years. In the study of Truong et al[5], postoperative radiotherapy rates, in patients stage I EC with > 50% myoinvasion, varied widely by age from 97% (age 65-74 years) to 74% (age > 75 years), age rather than PS or comorbidity was found to be the major reason for non-standard management in elderly patients. However, no significant difference was found in treatment tolerance for surgery and radiotherapy. In the study of Vaknin et al[19], the morbidity of hysterectomy elderly women appears to be acceptable. Toxicity for pelvic radiotherapy was studied by Pignon et al[20] and in the subgroup of patients with endometrial cancer, the probability to suffer from > grade 2 side-effects was not significantly different between the age-groups. In contrast, randomized clinical trials clearly demonstrated that elderly high-risk patients who were treated with adjuvant RT had a favorable outcome, suggesting a benefit to adjuvant RT in these women[6,21]. Despite the efficacy and safety of surgery and adjuvant radiotherapy, elderly women with EC are less likely to receive a complete treatment program. The consequences of this substandard approach were that the proper role of potentially curative therapy in the treatment of older and oldest EC women remained a question issue in geriatric oncology. Furthermore, Fleming et al[22] compared retrospectively 338 patients in two groups based on age at diagnosis, who underwent surgery and adjuvant radiotherapy, also evaluated according

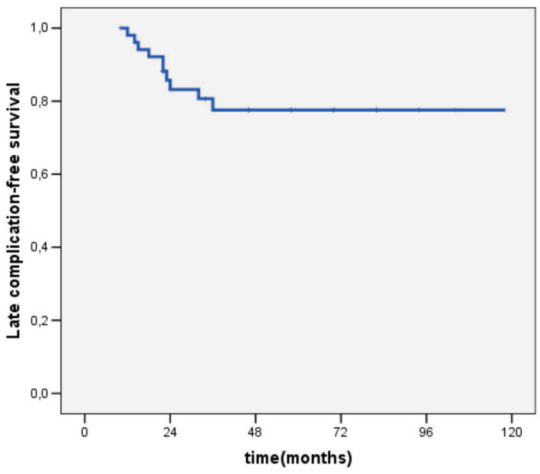

Figure 3. Late complication-free survival.

co-morbidity, and concluded that age ≥ 70 years alone may not be a significant variable affecting overall survival in patients with early stage EC.

Aim of the present study was to analyze our experience in the use of adjuvant radiotherapy applied routinely in older and oldest EC patients. The crude overall survival and disease specific survival at 5-years were respectively 72.3% and 90%.

These rates are similar to those of published phase 3 trials[6,21], and the old age was not a significant prognostic factor for survival in our study.

Consequently, we believe that an evaluation of co-morbidities in a group of older patients could help in elucidating the prognostic effect of each factor. Multiple co-morbidities are common in elderly cancer patients and can affect cancer stage at presentation and survival[23]. Co-morbidities were retrospectively classified applying ACE-27[10] to the case notes of patients receiving radiotherapy for endometrial. The ACE-27, a validated chart-based co-morbidity index, was especially created to describe co-morbidity for patients with cancer. We found high frequency of co-morbidities (88.7%) in this series of older patients; however, the severity of disease as measured by ACE-27 was mild in most cases (58.5%). The most frequent co-morbidities were cardiovascular diseases (hypertension, congestive heart disease, arrhythmia, and myocardial infarction), diabetes mellitus, gastrointestinal and respiratory diseases, and renal insufficiency, which are common in geriatric populations.

In our study, none or mild co-morbidity assessed by ACE-27 score emerged as an independent predictor for better survival upon multivariate analysis. This finding suggested that if co-morbidity could be compensated (generally a mild co-morbidity), then the patient would receive the standard treatment offered to patients without co-morbidities. The increasing severity of co-morbidity may sufficiently shorten the remaining life expectancy minimizing or negating the benefit of adjuvant radiotherapy. Furthermore, the ACE-27 index was not statistically associated with disease-free survival or recurrence in the multivariate analysis.

Our findings suggested the prognostic importance of co-morbidities and the potential value of including them in clinical studies in which overall survival is relevant. Overall, the present paper supports the opinion that radiotherapy after surgery can also be applied in elderly patients with EC owing to the well-tolerated toxicities and compliance. In all patients, the planned treatment was delivered and radiotherapy induced acute side effects in a high rate were as follows: diarrhea, nausea, urinary and skin complications. However, these rates were acceptable since patients suffered mainly from grade 1 toxicities, which can be managed successfully. No subjects had a toxicity level > grade 2. There is no evidence of increase of acute side effects regards radiotherapy, chemotherapy, co-morbidity and age. Delivering conformal radiation therapy routinely used in endometrial cancer women confers high doses to tumor target volumes in most elderly patients with a good or acceptable tolerance. An overall actuarial late complication-free survival of 77.6% at 60 months was found. The present study encompassed all types of late effects graded from 1 to 4. Globally, the late tolerance of elderly patients was not different from results in younger age groups, and as reported by our previous experience in this particular setting[24-26]. Moreover also the cancer-related fatigue was acceptable[27-29].

CONCLUSIONS

Our data showed that adjuvant radiotherapy after hysterectomy and bilateral salpingo-oophorectomy also maintains its activity and feasibility in elderly EC patients. It is difficult to determine a standard therapy for elderly patients based only on chronological landmarks, as the effects of aging depend on the individual. It is very important to assess co-morbidities with their severity in order to develop patients-tailored treatments. Whenever possible and appropriate, elderly women, correctly stratified for co-morbidity, should be allowed and encouraged to participate in clinical studies.

CONFLICT OF INTEREST STATEMENT:
None.

ACKNOWLEDGEMENTS
Grant support: The whole cost of the study was supported by our Institutions. The authors thank Paola Favetta for her support in the preparation and correction of the manuscript.

References

1. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, , based on November 2011 SEER data submission, posted to the SEER web site, April 2012.
2. Mundt AJ, Waggoner S, Yamada D, , Connell PP. Age as a prognostic factor for recurrence in patients with endometrial carcinoma. 2000; 79: 79-85.

3. Alektiar KM, Venkatraman E, Abu-Rustum N, Barakat RR. Is endometrial carcinoma intrinsically more aggressive in elderly patients? 2003; 98: 2368-2377.
4. Ahmed A, Zamba G, DeGeest K, Lynch CF. Gynecol Oncol 2008; 111: 35-40.
5. Truong PT, Kader HA, , Lesperance M, MacNeil MV, Berthelet E, McMurtrie E, Alexander S. The effects of age and comorbidity on treatment and outcomes in women with endometrial cancer. 2005; 28: 157-164.
6. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, De Winter KA, Lutgens LC, van den Bergh AC, van de Steen-Banasik E, Beerman H, van Lent M. Lancet 2000; 355(9213): 1404-1411.
7. Carreca I, Balducci L, Extermann M. Cancer in the older person. Cancer Treat Rev 2005; 31: 380-402.
8. Lichtman SM. Management of advanced colorectal cancer in older patients, Oncology (Williston Park) 2005; 19: 597-602.
9. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. Int J Gynecol Cancer 2009; 105: 103-104.
10. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel Jr EL. Prognostic importance of comorbidity in a hospital-based cancer registry. J Am Med Assoc 2004; 291: 2441-2447.
11. Fiorica F, Berretta M, Colosimo C, Berretta S, Ristagno M, Palmucci T, Palmucci S, Lleshi A, Ursino S, Fisichella R, Spartà D, Stefanelli A, Cappellani A, Tirelli U, Cartei F. Arch Gerontol Geriatr 2010; 51: 277-282.
12. Fiorica F, Berretta M, Ursino S, Fisichella R, Lleshi A, Fiorica G, Stefanelli A, Zini G, Tirelli U, Zanghi A, Cappellani A, Berretta S, Cartei F. Arch Gerontol Geriatr 2012; 55: 283-288.
13. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-214.
14. Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, Gonzales-Gonzales D, Horiot JC, Bolla M, Bartelink H. EORTC Late Effects Working Group, Late effects toxicity scoring: the SOMA scale. Int J Radiat Oncol Biol Phys 1995; 31: 104-1047.
15. Kaplan EI, Meier P. Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958; 53: 457-481.
16. Cox DR. Regression models and life tables (with discussion). J Roy Stat Soc B 1972; 34: 187-220.
17. Deligdisch L, Kase NG, Bleiweiss IJ. Endometrial cancer in elderly women: a histologic and steroid receptor study. Gerontology 2000; 46: 17-21.
18. . FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-1987 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. 1994; 10: 31-34.
19. Vaknin Z, Ben-Ami I, Schneider D, Pansky M, Halperin R. A comparison of perioperative morbidity, perioperative mortality, and disease-specific survival in elderly women (≥ 70 years) versus younger women (< 70 years) with endometrioid endometrial cancer. Int J Gynecol Cancer 2009; 19: 879-883.
20. Pignon T, Horiot JC, Bolla M, Van Poppel H, Bartelink H, Roelofsen F, Pene F, Gerard A, Einhorn N, Nguyen TD, Vanglabbeke M, Scalliet P. Age is not a limiting factor for radical radiotherapy in pelvic malignancies. Radiother Oncol 1997; 42: 107-120.
21. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, Pearlman A, Maiman MA, Bell JG; Gynecologic Oncology Group. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004; 92: 744-751.
22. Fleming ND, Lentz SE, Cass I, Li AJ, Karlan BY, Walsh CS. Is older age a poor prognostic factor in stage I and II endometrioid endometrial adenocarcinoma? Gynecol Oncol 2011; 120: 189-192.
23. Extermann M0. Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 2000; 35: 181-200.
24. Fiorica F, Stefanelli A, Fisichella R, Tirelli U, Berretta M. Eur Rev Med Pharmacol Sci 2012; 16: 1605-1606.
25. Fiorica F, Berretta M, Colosimo C, Stefanelli A, Ursino S, Zanet E, Palmucci T, Maugeri D, Malaguarnera M, Palmucci S, Grasso M, Tirelli U, Cartei F. Arch Gerontol Geriatr 2010; 51: 31-35.
26. Fiorica F, Cartei F, Carau B, Berretta S, Spartà D, Tirelli U, Santangelo A, Maugeri D, Luca S, Leotta C, Sorace R, Berretta M. Arch Gerontol Geriatr 2009; 49: 54-59.
27. Giacalone A, Spina M, Berretta M, Tirelli U. Br J Cancer 2012; 106: 424.
28. Giacalone A, Berretta M, Spina M, Tirelli U. J Clin Oncol 2012; 30: 4175.
29. Giacalone A, Quitadamo D, Zanet E, Berretta M, Spina M, Tirelli U. Support Care Cancer 2013; 21: 2899-2911.