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ORIGINAL ARTICLE

Real-world data on initial treatment strategies for older adult patients with endometrial cancer in Japan

Mayu Yunokawa[1,2] · Shinsuke Sasada[1,3] · Yae Takehara[4] · Kenta Takahashi[4] · Tatsunori Shimoi[1] · Kan Yonemori[1] · Mitsuya Ishikawa[4] · Tomoyasu Kato[4] · Kenji Tamura[1]

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Abstract

Objective Current strategies for the treatment of endometrial cancer in older adult patients require re-evaluation given the global trend in population aging, especially in Japan. We sought to evaluate initial treatment offered to older adult patients with endometrial cancer in Japan.

Methods We retrospectively analyzed data on the standard treatment by age group in patients with endometrial cancer who underwent surgery between January 2005 and December 2013 at the National Cancer Center Hospital (Tokyo, Japan). Patients were stratified into four groups according to age: a younger group, aged 64 years or younger; older adult group 1, aged 65–69 years; older adult group 2, aged 70–74 years; and older adult group 3, aged ≥75 years.

Results Among 551 patients with endometrial cancer diagnosed and treated at our hospital, data from 531 eligible patients were analyzed. The proportion of patients in the older adult groups 1 or 2 who received standard treatment was the same as in the younger group. However, significantly fewer patients in older adult group 3 received standard treatment compared with the younger group (26% vs. 71%, $p=0.0001$). Furthermore, the proportion of patients in older adult group 3 who underwent standard surgery was significantly lower than that in the younger group (26% vs. 72%, $p=0.0001$).

Conclusions The results indicate that age 75 years and older might represent a cutoff for the development of age-based treatment strategies for endometrial cancer. This information could be used to determine the upper age limit for participation in clinical trials in Japan.

Keywords Older adult · Endometrial cancer · Real-world data · Standard therapy

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries, including Japan [1], and its incidence peaks after the menopause, particularly in the late 50s. The population in Japan is aging at a faster rate than that of any other country in the world [2]. Therefore, it is necessary to evaluate current treatment strategies for older adult patients with cancer, including endometrial cancer.

The definition of an older adult patient can vary across studies and guidelines depending on the context and has, therefore, not been universally defined. The majority of developed countries, including Japan, have accepted 65 years as the definition of an older adult or older person, although this definition may not be applicable in developing countries [3]. Nevertheless, the definition of older age in the clinical setting of the treatment of cancer has yet to be confirmed.

The age-related decline in multiple physiological and psychological systems is generally referred to as frailty. Individual differences in frailty among older adult patients are influenced by various factors including physiological distress, psychological problems, comorbidity, polypharmacy,

✉ Mayu Yunokawa
mayu.yunokawa@jfcr.or.jp

1 Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

2 Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation of Cancer Research, 3-8-31 Ariake, Koutou-ku, Tokyo 135-8550, Japan

3 Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan

4 Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan

and social background. Furthermore, the majority of clinical trials evaluating the efficacy of surgery or adjuvant therapy for patients with endometrial cancer have not established an upper age limit for participation or there has been no evidence-based consensus on upper age in clinical trials with an upper age limit [4–7]. Therefore, evidence-based standard initial treatment for older adult patients with endometrial cancer is the same as for younger patients. However, older adult patients have been under-represented in trials, and older adult patients eligible for participation in clinical trials were likely to meet specific eligibility and exclusion criteria [8]. Insufficient real-world data exist to evaluate treatment strategies by age for patients with endometrial cancer, and no clinically meaningful definition of older adult age for endometrial cancer treatment has been established.

To evaluate the actual initial treatment strategies for older adult patients with endometrial cancer in Japan and to determine a clinically meaningful definition of older adult age for each treatment modality, we retrospectively analyzed real-world data from a single institution regarding the numbers of patients receiving standard treatment by age group.

Patients and methods

Patients

The endometrial cancer database containing all patients treated at the National Cancer Center Hospital in Japan was used to identify all patients with endometrial cancer who underwent surgery between January 2005 and December 2013 at the National Cancer Center Hospital in Tokyo, Japan. We collected the information as a retrospective chart review. We excluded the following patients: patients receiving neoadjuvant chemotherapy; patients with distant metastatic cancer except peritoneal metastasis; patients with carcinosarcoma, or double cancer that affected the treatment strategy for endometrial cancer. Surgical staging was performed using the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system [9]. Estrogen-dependent endometrial cancer (type 1) was defined as G1 and G2 endometrioid adenocarcinoma and estrogen-independent (type 2) as G3 or non-endometrioid adenocarcinoma [10].

In the present study, older adult patients were defined as those older than 65 years of age, based on a report by the World Health Organization indicating that the age of 60 or 65, roughly equivalent to retirement age in most developed countries, can be considered the beginning of old age [3]. Patients were stratified into four groups based on age: a younger group, aged 64 years or younger; an older adult group 1, aged 65–69 years; an older adult group 2, aged 70–74 years; and an older adult group 3, aged 75 years or older.

The institutional review board of the National Cancer Center Hospital approved this study (IRB No. 2015-259). Informed consent was not required because of its retrospective nature.

Surgical procedure and adjuvant chemotherapy

Table 1 shows the standard of care for endometrial cancer at our institution (Table 1), which is based on extensive evidence on the treatment of endometrial cancer gathered

Table 1 Standard therapy for endometrial cancer in our hospital

FIGO stage				Pelvic lymph node	Para-aortic lymph node	Option for operation	Chemotherapy
IA	EM G1/2	Hysterectomy	BSO	None or biopsy	None or biopsy	Omentectomy[b]	None
	EM G3 or other	Hysterectomy	BSO	Dissection	None or biopsy	Omentectomy[b]	None
IB		Hysterectomy	BSO	Dissection	None or biopsy	Omentectomy[b]	None
II		Radical hysterectomy	BSO	Dissection	None or biopsy	Omentectomy[b]	None
IIIA		Hysterectomy[a]	BSO	Dissection	None or biopsy	Omentectomy[b]	AP
IIIB		Radical hysterectomy	BSO	Dissection		Omentectomy	AP
IIIC		Hysterectomy[a]	BSO	Dissection	Dissection	Omentectomy	AP
IVA		Hysterectomy[a]	BSO	Dissection	Dissection	Omentectomy ± cystectomy and/or rectal resection	AP
IVB		Hysterectomy[a]	BSO	Dissection[c]	Dissection[c]	Omentectomy	AP

AP doxorubicin/cisplatin combination regimen

[a]If there was cervical invasion, radical hysterectomy was performed

[b]If peritoneal cytology was positive in perioperative diagnosis, omentectomy was performed

[c]If complete resection was possible, pelvic and para-aortic lymphadenectomy was performed

in accordance with the guidelines established by the Japan Society of Gynecologic Oncology [17]. Neither the standard of care for endometrial cancer nor the Japan guidelines changed during the study period.

All patients underwent at least an abdominal total hysterectomy and bilateral salpingo-oophorectomy. Radical hysterectomy was performed for patients with suspected cervical stromal invasion or parametrial invasion. In cases of inter-half myometrial invasion and type 1 disease, we omitted pelvic lymph-node sampling without pelvic lymph-node dissection. Pelvic and para-aortic lymphadenectomy were performed when lymph-node metastases were detected on preoperative examination, intraoperative findings, or frozen sections. Complete pelvic lymph-node adenectomy was defined as the resection of > 20 pelvic lymph nodes, and complete para-aortic lymphadenectomy was defined as the resection of > 15 para-aortic lymph nodes. Peritoneal lavage cytology was routinely performed, and omentectomy was performed in patients with non-endometrioid adenocarcinoma or positive peritoneal cytology.

Adjuvant chemotherapy was performed in patients with FIGO stage III or IV disease. A doxorubicin and cisplatin combination regimen (AP regimen) (doxorubicin 60 mg/m^2 day 1, cisplatin 60 mg/m^2 day 1, every 21 days; 6 cycles) was given as the standard treatment for endometrial cancer. A paclitaxel and carboplatin combination regimen (TC regimen) (paclitaxel 175 mg/m^2 day 1, carboplatin AUC = 6 day 1, every 21 days; 6 cycles) was used as a less toxic regimen.

During the study period, a total of approximately ten gynecologists performed the surgery while approximately five medical oncologists administered the chemotherapy.

Statistical analysis

We analyzed the frequency of various aspects of the standard therapy undergone by patients. For the purposes of this study, "standard therapy" indicated complete compliance to therapy, regardless of the number of cycles of chemotherapy; moreover, we were unable to specify changes in chemotherapy.

Frequencies were compared using Fisher's exact test for categorical variables. Values of $p < 0.05$ were considered statistically significant. SPSS version 17.0 (SPSS, Chicago, IL, USA) was used for all analyses.

Results

Patients' characteristics

Among the 551 patients diagnosed with endometrial cancer and treated at our hospital, data from 531 eligible patients were analyzed (Fig. 1). Patients' characteristics are shown in Table 2. Regarding previous illnesses or complications, the incidences of breast cancer (diagnosed as a history of cancer), diabetes, hypertension, and dementia were significantly higher in older adult group 3 compared with the younger group. FIGO stage I or II disease was significantly lower in older adult group 3 compared with the younger group. The incidence of type 2 endometrial cancer was significantly higher in older adult groups 2 and 3 compared with the younger group.

Standard treatment among older adult groups

Patients in older adult groups 1 and 2 received standard treatment in the same proportion as in the younger group.

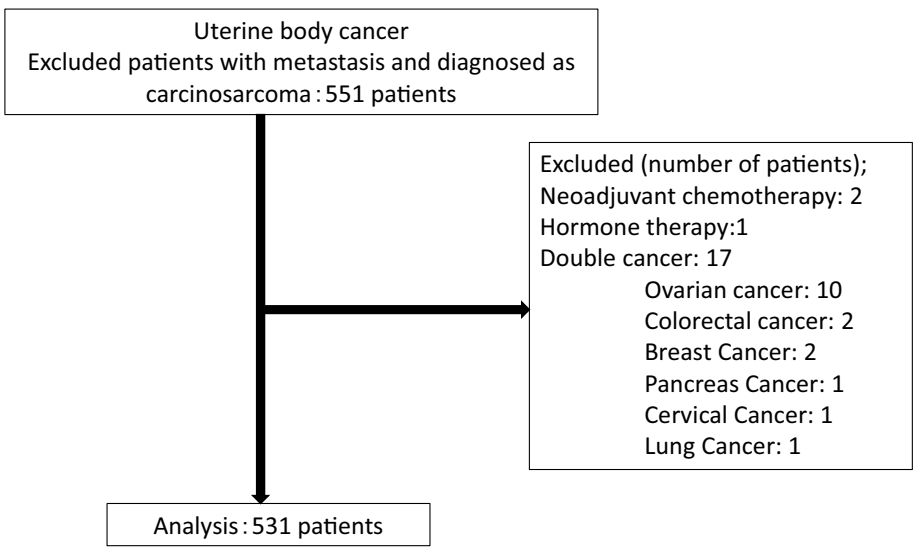

Fig. 1 Patient selection flow diagram

Table 2 Patients' characteristics

	Younger group ($n=426$)	Older adult group 1 ($n=53$)	Older adult group 2 ($n=33$)	Older adult group 3 ($n=19$)
	No. (%)	No. (%)	No. (%)	No. (%)
Age [range] (year)	54 [27–64]	67 [65–69]	72 [70–74]	79 [75–88]
Major past illness or complications				
Malignancies[a]	51 (12)	8 (15)	8 (24)	4 (21)
Breast cancer[a]	29 (7)	6 (11)	4 (12)	4 (21)*
Cardiovascular disease without hypertension	7 (2)	1 (2)	1 (0.4)	2 (10)
Hypertension	54 (13)	16 (30)*	11 (33)*	7 (37)*
Diabetes	19 (4)	5 (9)	3 (9)	4 (21)*
Dementia	0 (0)	0 (0)	0 (0)	1 (5)*
Body mass index [range], kg/m^2	22 [15–42]	24 [17–39]	23 [14–32]	22 [16–30]
FIGO stage (2009)				
I	340 (80)	47 (89)	30 (91)	8 (42)*
II	23 (5)	0 (0)	0 (0)	5 (26)*
III	55 (13)	4 (8)	3 (9)	4 (21)
IV	8 (2)	2 (4)	0 (0)	2 (11)
Pathological diagnosis				
Type 1	336 (79)	35 (66)	20 (61)[a]	8 (42)*
Type 2	90 (21)	18 (34)	13 (39)[a]	11 (58)*
Malignant peritoneal cytology	92 (22)	8 (15)	5 (15)	4 (21)

*Significantly higher or lower incidence compared with the younger group ($p<0.05$)

[a]Number of patients with a history of cancer

Table 3 Percentage of standard therapy in each group

Patients	Younger group	Older adult group 1	Older adult group 2	Older adult group 3
	No. (%)	No. (%)	No. (%)	No. (%)
All patients	426	53	33	19
Underwent standard therapy	303 (71)	36 (68)	21 (64)	5 (26)*

*Significantly higher or lower incidence compared with the younger group ($p<0.05$)

However, the proportion of patients who received standard treatment was significantly lower in older adult group 3 compared with the younger group (26% vs. 71%, $p=0.0001$) (Table 3).

Surgery among older adult groups

Patients in older adult groups 1 and 2 underwent standard surgery in the same proportion as in the younger group. However, the proportion of patients who underwent standard surgery was significantly lower in older adult group 3 compared with the younger group (26% vs. 72%, $p=0.0001$) (Table 4).

No patients in older adult group 3 underwent radical hysterectomy, even when cervical invasion was present. Pelvic lymphadenectomy tended to be performed less frequently in older adult group 2 (39% vs. 51%, $p=0.054$) and significantly less frequently in older adult group 3 (0% vs. 51%, $p=0.0002$) compared with the younger group (Table 4).

Chemotherapy among older adult groups

Standard chemotherapy was performed at almost the same frequency in older adult group 1 and the younger group. However, patients in older adult groups 2 and 3 were less likely to undergo chemotherapy, although the difference was not statistically significant (17%, 67%, 50%, Table 5). Changes in chemotherapeutic regimens were significantly more frequent in older adult group 3 than in the younger group (34% vs. 3%, $p=0.0354$) (Table 5).

Discussion

This study evaluated the proportion of older adult patients with endometrial cancer who received standard treatment compared with younger counterparts at a National Cancer Center in Japan. Older adult patients (those aged 75 years or older) were less likely to receive standard treatment

Table 4 Percentage of surgery in each group

	Younger group No. (%)	Older adult group 1 No. (%)	Older adult group 2 No. (%)	Older adult group 3 No. (%)
Intended surgery	426	53	33	19
Underwent standard surgery	307 (72)	36 (68)	22 (67)	5 (26)*
Intended radical hysterectomy	26	0	0	5
Underwent radical hysterectomy	19 (27)	–	–	0 (0)*
Intended pelvic lymphadenectomy	185	28	18	13
Underwent pelvic lymphadenectomy	95 (51)	18 (64)	7 (39)**	0 (0)*
Intended para-aortic lymphadenectomy	38	6	1	2
Underwent para-aortic lymphadenectomy	22 (58)	1 (17)	1 (100)	0 (0)

*Significantly higher or lower incidence compared with the younger group ($p < 0.05$); **$p = 0.054$

Table 5 Percentage of chemotherapy in each group

	Younger group No. (%)	Older adult group 1 No. (%)	Older adult group 2 No. (%)	Older adult group 3 No. (%)
Intended chemotherapy	63	6	3	6
Underwent standard chemotherapy	50 (79)	5 (83)	1 (33)	1 (16)*
Omit chemotherapy	11 (17)	1 (17)	2 (67)	3 (50)
Change in chemotherapy regimen	2 (3)	0 (0)	0 (0)	2 (34)*

*Significantly higher or lower incidence compared with the younger group ($p < 0.05$)

than those in a younger group (aged 64 years or younger), although standard treatment was given at the same frequency in older adult patients (aged 65–74 years) as in the younger group. These findings provide meaningful basic information to understand real-world situations of therapy for older adult patients with endometrial cancer, although the numbers in the older groups, especially older group 3, were very small, representing a sizeable limitation to our study.

To date, no randomized clinical trial has been performed in older adult patients with endometrial cancer to determine the optimal surgical procedure or adjuvant therapy for this group [4–6]. Although it is considered important to implement standard treatment appropriate for older adult patients as well as younger patients to ensure efficacy, treatment strategies for patients with endometrial cancer are not distinguished by age. However, older adult patients generally have more physiological distress, psychological problems, multiple comorbidities, polypharmacy, and poor social background than younger counterparts. Individual differences also exist among older adult patients. Some non-fit, potentially vulnerable, or frail older adult patients are unable to undergo standard treatment, and instead receive less toxic treatment or best supportive care. However, no reports of the percentage of older adult patients receiving standard initial treatment or less toxic initial treatment are available. In the present study, approximately 25% of patients aged 75 or older received standard treatment, including surgery and chemotherapy, although almost 70% of older adult patients aged 65–74 underwent standard treatment, a similar proportion to that in the younger patient group. These results suggest that the percentage of vulnerable or frail patients was significantly increased in the group older than 75, and that age over 75 was the key factor determining the initial treatment strategy for endometrial cancer. Unfortunately, no data were available on the proportion of patients who did not receive any treatment or received only best supportive care in our study, as we collected data only from patients who underwent surgery for endometrial cancer and did not evaluate the feasibility of the initial treatment. We were, therefore, unable to determine the percentage of very frail patients who could not be considered for surgery in our real-world study population. Moreover, since there is no nationwide database of surgery referrals in Japan, we have some way to go before grasping the real-world situation.

In the present study, we analyzed differences in comorbidities and nutritional condition, such as major previous illnesses or complications including cardiovascular disease, hypertension, diabetes, and dementia; and differences in nutritional status by body mass index. The proportion of patients with a history of breast cancer, diabetes, or dementia was significantly higher in the group aged over 75 years while the proportion of patients with hypertension was higher in those over 65 years of age compared with the

younger patient group. However, nutritional status did not differ according to age.

The frailty or vulnerability of older adult patients with cancer requires evaluation at the pre-treatment stage to avoid inappropriate management during treatment. Geriatric assessment is one tool that can be used to evaluate an older person's medical, psychosocial, and functional capabilities toward development of a coordinated and integrated plan for treatment and long-term follow-up [11]. A major limitation of this study was that we could not establish the frailty or vulnerability of older adult patients with endometrial cancer using geriatric assessment. In 2005, the International Society of Geriatric Oncology (SIOG) recommended that the assessment of vulnerability or frailty in older adult patients with cancer should include functional status, cognition, and mood [12]. Geriatric assessment is considered to select the appropriate treatment strategy for older adult patients [11, 13, 14]. By evaluating patients using geriatric assessment prospectively, it may be possible to select the appropriate surgical procedure or adjuvant therapy.

Surgery is the main therapeutic modality for the diagnosis and treatment of patients with endometrial cancer [15, 16]. FIGO staging and risk assessment for relapse are determined according to clinicopathological factors evaluated after surgery that may include total hysterectomy, bilateral oophorectomy, and pelvic and para-aortic lymphadenectomy [15–17]. We actively performed pelvic-only or pelvic and para-aortic lymphadenectomy for high-risk patients with deep myometrial invasion, cervical invasion, and type 2 histology in early-stage or advanced-stage disease for the purpose of diagnosis and treatment. A study of the Treatment of Endometrial Cancer (ASTEC) trial and an additional study previously showed that pelvic adenectomy did not prolong overall survival (OS) compared with no lymphadenectomy in early-stage endometrial cancer [18, 19]. However, one important reason for these findings was the low numbers of resected pelvic lymph nodes in the pelvic lymphadenectomy group. By contrast, results from the Survival Effect of Para-aortic Lymphadenectomy in Endometrial Cancer (SEPAL) study showed that OS was significantly longer in the pelvic and para-aortic lymphadenectomy group than in the pelvic lymphadenectomy group [20]. This study defined the lower limit of the number of resected para-aortic lymph nodes as 15. In the present study, we defined the standard complete pelvic lymphadenectomy as resection of > 25 pelvic lymph nodes, and complete aortic lymphadenectomy as resection of > 15 para-aortic lymph nodes. Therefore, the rate of pelvic or para-aortic lymphadenectomy was lower than that previously reported, even in the younger patient group (approximately 75% in a previous report vs. 51% in the current study) [21].

Standard adjuvant therapy for patients with advanced-stage disease treated at our institution was chemotherapy with an AP regimen. The Gynecologic Oncology Group (GOG) 122 trial was conducted to compare the AP regimen with whole-abdominal irradiation (WAI) in terms of progression-free survival (PFS) and OS [5]. In the GOG 122 trial, 152 patients (38%) aged 61–70 years and 82 patients (21%) aged 71 years or older participated, and chemotherapy was associated with better PFS and OS compared with WAI in any age group in a subgroup analysis. These results suggest that the standard adjuvant therapy for endometrial cancer is chemotherapy with AP, including in older adult patients. Our findings show that the proportion of patients older than 75 years receiving standard treatment for endometrial cancer was significantly lower than that of younger patients, although older adult patients under 75 years received standard treatment in similar proportion to younger patients. The AP regimen might be not feasible for patients older than 75, although there was a limitation because we did not analyze the reason why the AP regimen could not be administered.

Most patients with endometrial cancer are diagnosed at an early stage, leading to a good prognosis and favorable OS [22]. Several descriptive analyses from Western countries have reported that patients diagnosed with endometrial cancer were at increased risk of cardiovascular disease because of obesity and comorbidities [23, 24]. Recent reports have suggested that racial disparities can affect clinical characteristics and prognosis among patients with endometrial cancer [25, 26]. Some differences in treatment methods for patients with endometrial cancer are apparent between Japan and Western countries. Adjuvant chemotherapy appears to be more frequently performed in Japan, with adjuvant radiotherapy preferred in Western countries [27, 28]. These observations suggest that the country-level treatment strategy for older adult patients with endometrial cancer should be developed based on real-world evidence. The results of our study indicate that age 75 and older might represent a cutoff point for the development of age-based treatment strategies for endometrial cancer, and that this information could be used to determine the upper age limit for participation in clinical trials in Japan. Moreover, future prospective studies are required to clarify the frailty or vulnerability of older adult patients with endometrial cancer using factors other than age.

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Author contributions MY, SS, YT, KT participated in the data collection. MY performed statistical analysis and drafted the manuscript. TS, KY, MI, TK carried out operations or chemotherapy in the study period and helped to draft the manuscript. KT helped to draft the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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