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Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older

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Abstract

Objectives—To determine if readily obtainable markers of frailty predict disease-free survival (DFS) in elderly women with endometrial cancer treated with curative intent.

Methods—88 consecutive women age 60 treated with surgery, chemotherapy and radiation for Stage I–IV endometrial cancer were included. We considered the following health deficits as markers of “frailty”: albumin < 3.5 mg/dL, hemoglobin < 10 mg/dL, BMI < 20 kg/m², unintentional weight loss, ECOG performance status ≥ 2, history of osteopenia or osteoporosis and Charlson comorbidity score. Kaplan Meier estimates and Cox proportional hazards models of DFS were calculated.

Results—The median age was 68.5 (range 60–88 years). The majority of women (65/88) had at least one frailty factor at baseline and 23/88 had two or more. All women received radiation and chemotherapy. Treatment was delayed, modified or truncated in 46% (40/88) of women due to treatment-related toxicity. Age (< 70 vs. ≥ 70 y) did not independently predict toxicity or recurrence risk. Women with at least one baseline frailty factor had twice the risk of disease recurrence (HR=2.21;95% CI: 1.02–4.80) when adjusted for age, stage, grade and Charlson score. The 3-year DFS was 77% in those with no frailty markers and 48% in those with at least one (p=0.02). The presence of a frailty marker also predicted shortened overall survival (HR=2.34;95%CI: 1.08–5.03) irrespective of treatment administered and stage of disease.

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Conclusions—A combined frailty measure was a more robust predictor of DFS and OS than patient age, tumor characteristics and comorbidities in this cohort of older women with very good functional status.

Keywords

Endometrial cancer; radiation therapy; chemotherapy; elderly; frailty

Introduction

Older women with endometrial cancer have substantially poorer prognosis than younger patients [1, 2]. Increasing age is associated with more aggressive tumor characteristics, making older women more likely to require radical therapy, a combination of surgery, chemotherapy and radiation, to increase their chance of cure [3]. However, older women with high-grade endometrial cancer are far less likely to receive radical therapy than younger women with highgrade disease [4]. Concerns about treatment-related toxicity and unclear benefit are major drivers of this disparity [5], but the role of age as a prognostic factor remains controversial.

A number of studies of adjuvant radiation therapy in early stage, high risk endometrial cancer have found that age over 60 or 70 is an independent risk factor for poor outcomes [3, 6]. More recently, another group found that age > 70 no longer predicted progression-free or disease-specific survival in early stage endometrial cancer after accounting for differences in histology and age-related comorbidity [7]. Similarly, a study including 1,182 patients undergoing treatment for stage I-III endometrial cancer over age 70 found that progression-free survival was no different in older patients after risk-adjustment for age-related health deficits [8]. Age is also commonly thought to predict poor tolerance of adjuvant therapy in women with endometrial cancer, but there is growing evidence that radical therapy is both tolerable and safe in selected older patients [9–11]. Together, this evidence suggests age-related conditions and deficits, not age itself, should be used to weigh the risks and benefits of adjuvant treatment.

Frailty can be conceived of as a progressive accumulation of deficits in health status, including comorbidities, abnormal laboratory tests, functional impairments and disabilities [12]. Comprehensive assessment of these domains can identify a frail population at risk for severe toxicity, as well as a robust group that are likely good candidates for standard treatment [13]. The National Comprehensive Cancer Network recommends the incorporation of frailty assessment into the routine care of older cancer patients, to help individualize therapy for the very heterogeneous older population [14]. We have shown in prior work that markers of inflammation such as albumin and self-reported ability to take a long walk are more powerful predictors of survival than disease-specific factors in older patients with hematologic malignancies [15, 16].

Though trials have assessed outcomes of regimens that combine surgery, radiation, and chemotherapy, little information is available specifically focusing on the treatment of older women with endometrial cancer [17, 18]. Combined modality therapy with chemotherapy and radiation has been shown to decrease both local and distant recurrence, but is associated

with significant toxicity, even in younger women [18]. The goal of this study was to determine if readily obtainable markers of frailty could predict treatment tolerability, recurrence or overall survival in a consecutive group of older women with high-risk endometrial cancer who received radical therapy.

Methods and Materials

Baseline characteristics

Between 1982 and 2011, 95 consecutive women over age 60 were treated with radical therapy for Stage I-IV endometrial cancer at Dana/Farber-Brigham and Women's Cancer Center. Of these, 88 met the eligibility criteria, i.e., they had stage I-IV disease treated with a hysterectomy and bilateral salpingoophorectomy, with or without pelvic and para-aortic lymph node dissection, followed by radiation and chemotherapy. Patients were staged based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines.

Clinical data were abstracted from the medical and radiation therapy (RT) records with approval of the Institutional Review Board. We extracted clinical characteristics and outcomes from medical records and calculated a baseline Charlson comorbidity score. Baseline characteristics were collected for all patients, and included date of diagnosis, age at diagnosis, grade, histology, FIGO stage, and socioeconomic factors as listed in Table 1. We considered the following markers of "frailty": albumin < 3.5 mg/dL, hemoglobin < 10 mg/dL, BMI < 20 kg/m², unintentional weight loss, ECOG performance status ≥ 2, and history of osteopenia or osteoporosis.

Eligible patients were treated with external beam radiation (EBRT) and underwent a CT simulation followed by conformal treatment. Data regarding chemotherapy use and type of chemotherapeutic agent used were also recorded.

Clinical endpoints

Patients were followed for a median of 3.18 years (range 0.45 – 15 years) for disease related clinical endpoints and post-treatment adverse events. We recorded whether treatment was delayed, modified or truncated. Actuarial estimates of disease-free survival (DFS), and overall survival (OS) were assessed, and were stratified by the presence of frailty markers.

Statistical Analysis

We report medians or mean with standard deviation for numeric variables and percentages for categorical or ordinal variables. Treatment groups were compared using exact Wilcoxon test for numeric or ordinal variables, Fisher exact test for binary variables, and likelihood ratio test for multi-category discrete variables. 2-sided *p*-values < 0.05 were considered statistically significant. Disease free survival was defined as the time from the start date of treatment to failure or death, whichever occurred first. Overall survival was measured from the date of the start of radiation therapy to the date of death or date of last follow-up. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox regression analyses were used to identify

predictors of OS and DFS. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Cary, NC)

Results

The baseline characteristics of the 88 recipients of radical therapy are displayed in Table 1. The median age of the cohort was 68.5 years, with a range of 60–88 years. The majority of women (67.8%) had stage III or IV disease, while 32.2% had stage I or II disease with high-risk features. Most tumors were high-grade (67/88). The most common histology was papillary serous (64.7%), followed by endometrial adenocarcinoma (18.2%), endometrioid carcinoma (6.8%), clear cell carcinoma (5.7%) and carcinosarcoma (4.6%). Women 70 and older did not have substantially more Grade III histology or advanced stage disease than women < 70.

Almost all women had an excellent functional status; the ECOG PS score was 0 in 81.6% (72/88), 1 in 16.1% and 2 in 2.3%. There was a low prevalence of comorbidities, with only 35% of women having a Charlson score of 2 or greater. In contrast, 73.9% of women had at least one of the frailty factors at baseline, as shown in Figure 1. Women younger than 70 years were not substantially less likely to have a frailty factor than women 70 or older (56.3% vs. 65%, $p=0.40$).

The majority of chemotherapy regimens included two (64/88) or three drugs (11/88). The most common regimens were carboplatin/taxol (58/88), carboplatin/taxol/adriamycin (10/88) and single agent carboplatin (5/88). Treatment was associated with significant toxicity. Almost all women (94.3%) experienced some toxicity, with 32 women (36.4%) experiencing grade 3 or 4 toxicity at least once during therapy with RT and chemotherapy. GI toxicity was present in 76.1% of women, GU toxicity in 13.6%, and other types of toxicity in 85%. One-third of women required an unscheduled visit to the emergency room and/or hospitalization during treatment. Treatment was delayed in 18 women (20.5%), dose-reduced or otherwise modified in 40 (46%), and stopped early in 12 (13.6%). There was no substantial difference in rates of grade III-IV toxicity, modification or truncation of therapy, or ED visits and/or hospitalizations by age (< 70 vs. 70 or greater) or frailty score (no frailty vs. 1 or more frailty factor).

The median survival of the cohort was 7.27 years (range 0.44 to 15.00 years). Thirty-eight women had progression or recurrence of disease, and there were 39 deaths. DFS for the entire population was 88% at 1 year, 60% at 3 years and 56% at 5 years. DFS and OS for patients with and without a frailty factor are shown in Figure 2. The 3-year DFS was 77% in those with no frailty markers and 48% in those with at least one ($p=0.02$). Univariate analyses of survival are presented in Table 2 and multivariable models in Table 3. Women with at least one baseline frailty factor had twice the risk of disease recurrence ($HR=2.21$; 95% CI: 1.02–4.80) when adjusted for age, FIGO stage, tumor grade and Charlson comorbidity score. The presence of a frailty marker also predicted shortened overall survival ($HR=2.34$; 95% CI: 1.08–5.03) irrespective of treatment administered and stage of disease. When we limited the analysis to patients who had a normal performance status (ECOG

PS=0), the frailty score still robustly predicted disease recurrence (HR=2.33; 95%CI: 1.04–5.23).

Discussion

Though the vast majority of women diagnosed with endometrial cancer are postmenopausal, information about the tolerability and outcomes of radical therapy in older women is scarce. Our results help to fill this knowledge gap in a number of ways. First, the 5-year survival in this group of women aged 60 and older is comparable to estimates that include younger women. Second, age in itself was not a predictor of tolerability of therapy, recurrence or mortality in our cohort. Finally, we were able to show even in this highly selected group of patients that a simple frailty score was a more valuable predictor of disease-free and overall survival than the traditional risk factors of age, tumor characteristics and comorbidities.

Advancing age is a known prognostic factor for endometrial cancer. In the PORTEC randomized trials, age over 60 has been used as a sign of worse prognosis; therefore, we selected a cut-off of 60 years old for this analysis [19]. Other studies have reported that outcomes after primary treatment for endometrial cancer are worse with increasing age but none have adjusted their analyses for age-related deficits.[20, 21] In addition, age is thought to adversely impact those with high-grade disease. We limited our analysis to women who were treated radically with chemotherapy and radiation, the majority of whom had uterine papillary serous histology. Patients received a recommendation to receive a combination of radiation therapy and chemotherapy in an attempt to address the high risk of recurrence [21]. One retrospective analysis of 280 elderly (≥ 70 years old) women with endometrial cancer found that only 53% of elderly women who were recommended chemotherapy and radiation received treatment [5]. Molecular genomic analysis recently classified papillary serous carcinoma as more similar to high-grade endometrioid carcinoma [22]. We also included advanced stage, high-grade endometrioid cancer patients and adjusted on multivariable analysis for known prognostic features.

Aging is the result of the accumulation of molecular and cellular damage over time, eventually leading to a state of vulnerability. This accumulation of molecular deficits translates into an increasing number of problems in health status. Frailty describes a state in which physiologic reserve is depleted to the point that even small stressors can result in poor outcomes, including delirium, falls, disability and death [23]. The distribution of health deficits in the older population is very wide, making it necessary to individualize plans of care. Although the oncology community has long recognized the value of performance status, a relatively crude measure of physical function, comprehensive geriatric assessment includes many other domains, such as disability, cognition, mood and social support.

Our frailty score is not based on a multidimensional patient evaluation; rather, we used readily available markers of health status referable to multiple geriatric domains. We decided not to include many comorbidities in our frailty score, as we wanted to see what our index added to a widely-used method of adjustment for comorbidity. Despite its simplicity, the frailty score was able to readily identify patients at risk for worse outcomes, even in this highly selected population in which traditional markers of function and disability (such as

activities of daily living, falls and cognitive impairment) would have ceiling effects. It demonstrated the value of including health deficits that fall outside the traditional categories of cancer-specific risk factors, performance status and comorbidity.

A more ideal measure of frailty would be based on prospective patient assessment. Hurria et al. have shown that a modified comprehensive geriatric assessment (CGA) is feasible in an oncology clinic; its results predict both treatment tolerability and outcomes [13]. A 30–40 item frailty index based on geriatric assessment information from a broad spectrum of domains is a pragmatic way of measuring deficit accumulation, as demonstrated by Rockwood [24]. Health deficits, which can include symptoms, signs, disabilities and diseases, can differ by cohort as long as they are clearly age-related, do not saturate at too young an age, and cover a range of systems. Cutoffs that define frail, pre-frail and robust individuals seem to be consistent between populations. Cohen and Hurria recently used this method in their CGA cohort. Patients identified as frail by deficit-accumulation index were more likely to have serious toxicity, to be hospitalized, and to discontinue chemotherapy [25].

Incorporating modified geriatric assessment into the evaluation of older patients with gynecologic cancers and utilizing a cumulative deficit index would substantially enhance care and inform discussions about potential risks and benefits of treatment. If the value of accounting for frailty can be shown in this cohort of very fit women who received aggressive therapy, then it will be of much greater use in a general population with a higher prevalence of health deficits. There is also the possibility of identifying novel markers of frailty in this population. For example, routine abdominal and pelvic imaging can be used to detect sarcopenia, which has been shown to predict serious complications after surgery in patients with pancreatic cancer [26].

To our knowledge this is the first study to use a frailty score to risk adjust for DFS and OS in a cohort of older women receiving radical therapy for endometrial cancer. It is important to emphasize that our results are based on a single-institution study, and are a population of highly selected older women, many of whom were participating in clinical trials. Therefore, results may not be generalizable. However, the low frequency of health deficits in our population should have biased our results towards the null; a similar approach would likely be more predictive in a wider population of patients with endometrial cancer, not less. As mentioned above, we were limited in the number and type of health deficits we could use in this analysis as it was not based on prospective geriatric assessment. Our results serve as proof of concept for the utility of a cumulative deficit frailty index for use in gynecologic oncology. A limitation of our cohort is that accrual occurred over 30 years. During that time, methods of delivering radiation, as well as chemotherapy regimens, have improved. Thus, we consider a variety of regimens with varying levels of toxicity and efficacy.

Conclusions

In summary we found that radical therapy for high-risk endometrial cancer in this population of women 60 and older was associated with similar outcomes to younger women. A measure of frailty, not age, was the most accurate predictor of recurrence and survival. Therefore,

decisions to offer or decline curative therapy for endometrial cancer should not be based on age alone. Development of a frailty index in a population of patients with gynecologic cancers is an important area for future work.

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Highlights

- Older women receiving radical therapy had similar outcomes to younger women.
- Age in itself not a predictor of disease-free or overall survival.
- Markers of frailty predicted survival better than PS and tumor characteristics.

Figure 1.
Distribution of frailty indicators in 88 women with high-risk endometrial cancer.

Figure 2. Kaplan—Meier plot of overall (A) and disease-free (B) survival in 88 women with or without a frailty factor who received chemotherapy and radiation for endometrial cancer.

Table 1

Baseline Characteristics of 88 older women with endometrial cancer who received chemotherapy and radiation

Characteristic	N	(%)
Age at diagnosis		
60 to <70	48	54.5
70 to <75	30	34.1
75 to 82	10	11.4
Race		
Caucasian	70	79.6
Hispanic	8	9.1
African American	10	11.4
Lives alone	19	25.0
Education		
High school or less	14	16.0
Beyond high school	31	35.2
Unknown	43	48.9
Employed	19	21.6
ECOG-PS		
0	71	81.6
1	14	16.1
2	2	2.3
BMI (WHO categories)		
<20 kg/m ²	19	24.1
20–25 kg/m ²	32	40.5
>25 kg/m ²	28	35.4
Weight loss	12	13.6%
History of smoking	35	40.2%
Osteopenia/Osteoporosis	16	18.2%
Charlson comorbidity score		
0	25	28.7%
1	31	35.6%
2	18	20.7%
> 2	13	14.9%
Comorbidities		
HTN	48	54.5%

Characteristic	N	(%)
DM	14	15.9%
Previous Cancer	13	14.8%
Pulmonary	6	6.8%
CHF	4	4.5%
MI	3	3.4%
Depression or Anxiety	32	36.4%
FIGO Cancer stage		
I	22 [*]	25.3%
II	6	6.9%
III	50	57.5%
IV	9	10.3%
Tumor grade		
1	2	2.3
2	13	14.8
3	67	76.1
Unknown	6	6.8
Histology		
Papillary serous	57	64.7
Endometrioid adenocarcinoma	22	25
Clear cell carcinoma	5	5.7
Carcinosarcoma	4	4.6
Frailty score factors		
ECOG-PS 1	16	18.4
BMI < 20 kg/m ²	19	24.1
Unintentional weight loss	12	13.6
Albumin < 3.5 mg/dL	21	23.9
Hemoglobin < 10 mg/dL	14	15.9
Osteopenia/Osteoporosis	16	18.2

* Categories may not add up to 100% due to missing values

Table 2

Univariate analyses of risks for recurrence and all-cause mortality in 88 women who received chemotherapy and radiation for endometrial cancer

Patient Characteristic	Risk of recurrence HR (95%CI)*	Risk of death HR (95%CI)
Ages 70+	1.45 (0.77–2.71)	1.19 (0.61–2.34)
BMI < 20	0.56 (0.13–2.31)	0.97 (1.00–1.14)
Age at diagnosis	1.07 (1.01–1.13)	1.07 (1.01–1.13)
ECOG-PS > 0	1.86 (0.85–4.09)	0.99 (0.38–2.57)
Charlson Comorbidity Score	1.42 (0.69–2.91)	2.01(0.88–4.62)
Hgb < 10.0	1.68 (0.77–3.67)	1.57 (0.65–3.79)
Albumin < 3.5	2.20 (1.14–4.24)	1.89 (0.92–3.90)
Weight loss > 5% in 6 months	1.95 (0.89–4.24)	2.27 (1.03–5.03)
Osteopenia or osteoporosis	1.49 (0.72–3.06)	2.07 (1.00–4.33)
Stage III at diagnosis	1.22 (0.64–2.33)	2.00 (0.91–4.42)
Grade III at diagnosis	0.84 (0.41–1.73)	1.48 (0.61–3.56)
1 Frailty indicator present	2.48 (1.09–5.62)	2.39 (1.03–5.53)
> 1 Frailty indicator present	3.11 (1.35–7.19)	2.54 (1.05–6.14)

* Hazard ratios (HR) and 95% Confidence Intervals (95%CI) calculated by Cox proportional hazards models.

Table 3

Multivariable analysis of recurrence and death in 88 women who received chemotherapy and radiation for endometrial cancer

Health deficits	Risk of recurrence HR (95%CI)*		Risk of death from any cause HR (95%CI)	
	All women	Subset with ECOG=0	All women	Subset with ECOG=0
Frailty score 1	2.21 (1.02–4.80)	2.33 (1.04–5.23)	2.34 (1.08–5.03)	2.13 (0.95–4.79)
Age at diagnosis	1.07 (0.99–1.15)	1.06 (0.98–1.16)	1.06 (0.99–1.13)	1.05 (0.97–1.14)
Stage III at diagnosis (vs. all other stages)	0.72 (0.35–1.45)	1.73 (0.34–1.58)	1.02 (0.53–1.99)	1.05 (0.49–2.22)
High grade (vs. grade 1 or 2)	1.88 (0.75–4.74)	1.15 (0.39–3.37)	1.15 (0.53–2.52)	0.97 (0.35–2.70)
Charlson Comorbidity Score 1	1.06 (0.79–1.42)	0.98 (0.71–1.35)	0.93 (0.69–1.24)	0.93 (0.66–1.32)

* Hazard ratios (HR) and 95% Confidence Intervals (95%CI) calculated by Cox proportional hazards models.