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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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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.

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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/m,^{2} 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.

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.

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1. 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 high-grade 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

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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 1182 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.

2. Methods and materials

2.1. 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/m^2 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.

2.2. 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.

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%
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[a]	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

[a] Categories may not add up to 100% due to missing values.

2.3. 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

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