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Hormone replacement therapy after treatment for cervical cancer: Are we adhering to standard of care?

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HIGHLIGHTS

- 48% of patients received counseling for hormone replacement therapy (HRT).
- Older and uninsured patients were significantly less likely to receive HRT.
- Bone health maintenance practices were infrequently discussed or prescribed.

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ABSTRACT

Objective. The aim of this study was to assess hormone replacement therapy (HRT) and bone care health maintenance practices for cervical cancer patients with iatrogenic menopause, and, secondarily, to investigate the potential impact of specific demographic and clinical factors.

Methods. Women diagnosed with iatrogenic menopause due to cervical cancer treatment between January 1, 2005 and December 31, 2015 were identified from the University of Virginia's tumor registry. Univariable data were analyzed using Wilcoxon rank sum, Chi square, and Fisher's exact test; multivariable analysis was conducted using logistic regression.

Results. Two hundred and two women were included for analysis. Ninety-seven of these women (48.0%) received counseling and/or a prescription for HRT. After multivariable analysis, older age at diagnosis (adjusted OR 0.940, 95% CI 0.890–0.993, $p = 0.0270$) and uninsured payer status (adjusted OR 0.455, 95% CI 0.212–0.977, $p = 0.0435$) were associated with a decreased likelihood of receiving counseling or a prescription for HRT. A longer duration of follow-up was associated with the primary outcome with an adjusted OR of 1.011 (95% CI 1.001–1.020, $p =$ value 0.0252). Dual-energy X-ray absorptiometry scans (DEXA) were infrequent and received by only 17/197 (8.6%) of all women.

Conclusions. Fewer than half of all women received counseling and/or a prescription for HRT after diagnoses of iatrogenic menopause, and disparities were noted based on insurance status. These findings reflect a need for clearer guidelines on HRT during survivorship and improved efforts to reduce disparities in the distribution of survivorship care.

1. Introduction

There are approximately 13,000 new cases of invasive cervical cancer diagnosed each year in the United States; nearly 40% of cases are diagnosed in women under the age of 45 [1]. While fertility sparing surgery is an option for early stage disease (stage IA1–IB1), standard treatment involves either a radical hysterectomy with or without bilateral salpingo-ophorectomy or primary chemo-radiotherapy. Both treatments can result in premature ovarian failure. Studies suggest that a 2 Gray (Gy) radiation dose damages half of the oocyte population; doses greater than 6 Gy cause irreversible ovarian failure [2]. Ovaries may be preserved in the surgical management of squamous cell carcinoma (SCC) as the rate of metastasis is low (0.2% for stage IB and 2% for stage 2B); however, the risk of ovarian metastasis in adenocarcinoma is higher (approximately 5%), and bilateral oophorectomy is generally recommended [3–4]. Given that the average age of natural menopause is 51.3 years in the United States, the treatment of cervical cancer can result in early menopause for younger patients [5].

Menopause impacts quality of life as well as an array of important health outcomes, such as heart disease, osteoporosis, and overall mortality [6–7]. Surgical menopause may further increase a woman's

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lifetime risk of these aforementioned outcomes [8–9]. Fortunately, hormone replacement therapy (HRT) has been shown to ameliorate bothersome symptoms such as hot flushes and vaginal dryness and reduce the risk of hip and vertebral fractures, coronary heart disease (CHD) as well as overall mortality in younger, menopausal women [7,10–11]. Despite this, HRT is prescribed less frequently in gynecologic cancer survivors presumably due to concern for stimulating any residual malignant cells [12].

While evidence is limited, it suggests that use of HRT in survivors of cervical cancer is safe. SCC of the cervix is not known to be estrogen responsive although estrogen-receptor positivity has been found in approximately one-third of adenocarcinomas [13]. Two studies have failed to find that expression of estrogen and/or progesterone receptors is prognostic for cervical cancer patients [14–15]. Another trial did not find any difference in progression free survival (PFS) or overall survival (OS) between those who received and did not receive HRT [16].

In accordance with best practices, patients rendered menopausal by treatment should undergo health care maintenance focused on their bone health as well as be considered for hormone replacement to reduce negative health outcomes associated with premature ovarian failure. However, little is known about the use of HRT or bone health practices for cervical cancer survivors. Our objective was to assess HRT and bone care health maintenance practices for cervical cancer patients with iatrogenic menopause, and, secondarily, to investigate if certain demographic or clinical factors impact these practices.

2. Methods

After receiving approval by the University of Virginia's Institutional Review Board, a retrospective chart review was performed on all adult women (18 years or older) from January 1, 2005–December 31, 2015 with a diagnosis of cervical cancer. These patients were identified from the University of Virginia tumor registry. Inclusion criteria included documentation by the provider of pre-menopausal status prior to treatment for cervical cancer and, similarly, post-menopausal status after treatment. We excluded anyone without documentation of menopausal status at either time point. We abstracted the following information from the medical record: age, race, body mass index (BMI), smoking status (current, former, or never), date of diagnosis, date of last visit to a gynecologic oncologist, other medical problems, if the ICD-9 code for symptomatic menopausal state (627.2) was recorded, if counseling was provided for HRT, type of HRT provided (systemic and/or vaginal), dual-energy X-ray absorptiometry scans (DXA), prescription of vitamin D and/or calcium, total follow-up time, and date of first recurrence. We considered any documentation by the physician or any formulation of HRT on a medication list to be evidence of receiving a prescription for HRT. Total follow-up time was defined as time from diagnosis until last visit with a gynecologic oncologist.

The primary outcome was receiving counseling on and/or a prescription for HRT. Secondary outcomes included prescription of systemic HRT, prescription of vitamin D and/or calcium, and screening for osteoporosis with a DXA scan. SAS 9.3 was used for the statistical analysis. Wilcoxon rank sum test was used for the analysis of continuous variables. Chi-square or Fischer's exact tests were used to compare categorical variables. A logistic regression was performed to assess clinical and demographic factors associated with the primary outcome; predictors were chosen for the model if they were statistically significant after univariable analysis. A p-value of 0.05 or less was considered significant.

3. Results

Two hundred and two patients met inclusion criteria. The median age was 42 years, but patients ranged in age from 22 to 51 years. A majority of patients were white (75.7%), had private insurance (56.1%), had stage one disease (53.3%), and squamous histologic type (69.2%); the median follow-up time was 28.2 months. Ninety-seven patients (48.0%) received counseling and/or a prescription for some form of HRT. Of the 97 patients counseled on HRT, 80 (82.4%) ultimately received a prescription. Patient declination accounted for only 4 of the 17 women who were counseled but never received a prescription. Only 27 patients (13.4%) were assigned the diagnosis code for symptomatic menopausal state. Those counseled on and/or prescribed HRT were significantly younger with a median age of 40 versus 43 ($p = 0.0062$), more likely to have private insurance ($p = 0.0233$), more likely to have the ICD code for menopausal symptoms recorded in the chart ($p = 0.0007$), less likely to have a recurrence documented during follow-up ($p = 0.0294$), less likely to have had care at an outside hospital ($p = 0.0387$), and had earlier stage disease at diagnosis ($p = 0.0299$). In addition, those who received counseling had significantly longer

Table 1
Patient demographics stratified by receiving counseling or prescription for HRT.

Characteristic	Counseled on and/or prescribed HRT ($n = 101$)	Not counseled on and/or prescribed HRT ($n = 96$)	p-Value
Age (y) at diagnosis, median (Q1–Q3)	40.0 (36.0–44.0)	43.0 (38.0–46.5)	0.0062
Race			
White	84 (85.7)	68 (73.9)	0.0990
Black	11 (11.2)	3 (3.2)	
Other	3 (3.0)	21 (22.9)	
BMI, median (Q1–Q3)	28.3 (23.59–33. 61)	29.40 (25.30–36.28)	0.1912
Insurance, *n* (%)			
Uninsured	14 (13.9)	28 (29.2)	0.0233
Self-pay	3 (3.0)	0 (0.0)	
Medicaid	19 (18.8)	15 (15.6)	
Medicare	1 (1.0)	1 (1.0)	
Private	63 (62.4)	47 (49.0)	
Unknown	1 (1.0)	5 (5.2)	
Former smoker, *n* (%)			
No	86 (86.0)	82 (87.2)	0.8009
Yes	14 (14.0)	12 (12.8)	
Current smoker, *n* (%)			
No	60 (60.0)	57 (60.6)	0.9276
Yes	40 (40.0)	37 (39.4)	
Prior VTE, *n* (%)			
No	94 (93.1)	82 (85.4)	0.0819
Yes	7 (6.9)	14 (14.6)	
Cardiac disease, *n* (%)			
No	89 (93.9)	76 (79.2)	0.1531
Yes	12 (6.1)	20 (20.8)	
Any other cancers, *n* (%)			
No	98 (97.0)	93 (96.9)	0.9496
Yes	3 (3.0)	3 (3.1)	
FIGO stage, *n* (%)			
IA	5 (5.0)	7 (7.3)	0.0299
IB	61 (60.4)	44 (45.8)	
II	25 (24.8)	21 (21.9)	
III	9 (8.9)	16 (16.7)	
IV	1 (1.0)	8 (8.3)	
Histology, *n* (%)			
Squamous	69 (68.3)	69 (70.8)	0.3694
Adenosquamous	9 (8.9)	5 (5.2)	
Adenocarcinoma	19 (18.8)	17 (17.7)	
Neuroendocrine	4 (4.0)	3 (3.1)	
Other	0 (0.0)	3 (3.1)	
Recurrence, *n* (%)			
No	88 (87.1)	72 (75.0)	0.0294
Yes	13 (12.9)	24 (25.0)	
Care at outside hospital, *n* (%)			
No	82 (81.2)	60 (65.9)	0.0387
Yes	19 (18.8)	31 (34.1)	
Total follow-up time (m), median (Q1–Q3)	37.3 (17.5–65.8)	15.5 (7.3–41.3)	<0.0001

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