Gynecologic Oncology 136 (2015) 328–335

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# Survival advantage of marriage in uterine cancer patients contrasts poor outcome for widows: A Surveillance, Epidemiology and End Results study

William J. Lowery [a,b,*], Michael P. Stany [a,b], Neil T. Phippen [a,b], Kristen P. Bunch [a], Kate E. Oliver [a,1], Chunqiao Tian [c], G. Larry Maxwell [b,d], Kathleen M. Darcy [b], Chad A. Hamilton [a,b]

[a] Gynecologic Oncology Service, Department of OB/GYN, Walter Reed National Military Medical Center, Bethesda, MD, United States
[b] Department of Defense Gynecologic Cancer Center of Excellence, Women's Health Integrated Research Center at Inova Health System, Annandale, VA, United States
[c] Precision Therapeutics Inc., Pittsburgh, PA, United States
[d] Inova Fairfax Hospital, Falls Church, VA, United States

## HIGHLIGHTS

- Married women have a lower risk of death from uterine cancer than non-married counterparts.
- Among non-married patients, widows have a disproportionately high risk of dying from uterine cancer.
- Psychosocial interventions should be evaluated as part of adjuvant therapy and survivorship programs for widows.

## ARTICLE INFO

*Article history:*
Received 19 November 2014
Accepted 22 December 2014
Available online 26 December 2014

*Keywords:*
Uterine cancer
Survivorship
Relationship status
SEER

## ABSTRACT

*Background.* Marriage confers a survival advantage for many cancers but has yet to be evaluated in uterine cancer patients. We sought to determine whether uterine cancer survival varied by self-reported relationship status.

*Methods.* Data were downloaded from the Surveillance, Epidemiology, and End Results program for women diagnosed with uterine cancer (between 1991 and 2010 in nine geographic regions). Patients with complete clinical data for analysis were categorized as married, single, widowed or other (divorced or separated). Differences in distributions were evaluated using Chi-square, exact and/or Mantel–Haenszel test. Uterine cancer survival was analyzed by Kaplan–Meier method with log-rank test and multivariate Cox regression analysis.

*Results.* Of 47,420 eligible patients, 56% were married, 15% were single and 19% were widows. Married vs. non-married women had a higher likelihood of having low risk (grade 1/2 endometrioid) endometrial cancer and local disease ($p < 0.0001$), and a reduced risk of cancer death (HR = 0.8, 95% CI = 0.77–0.84). Multivariate evaluation of uterine cancer survival by relationship type indicated that widows consistently had significantly worse uterine cancer survival than single, married and other women in all patients and subset analyses ($p < 0.0001$).

*Conclusion.* While marital status is associated with differential uterine cancer survival, evaluation of self-reported relationship by type indicated that the poor outcome observed in widows explained most of the benefit attributed to marriage. This report identifies widows as a new high-risk subpopulation with significantly inferior outcomes potentially benefiting from personalized care and social support.

Published by Elsevier Inc.

## Introduction

Marital status is associated with a survival advantage among patients with a variety of cancers [1–5]. A recent study demonstrated that marriage conferred a survival advantage in the ten most lethal cancers in the United States as married patients were less likely to present with metastatic disease, more likely to receive definitive treatment, and less likely to die as a result of their cancer [2]. Among less lethal cancers, such as uterine cancer where the five-year overall survival rate is 82% [6], the impact of self-declared marriage and relationship status on cancer survival is uncertain. Favorable outcomes in uterine cancer are attributed to the fact that most cases are diagnosed at an early stage and aggressive histologic features are relatively rare

* Corresponding author at: 8901 Wisconsin Avenue, Bldg 19, room 3459, Bethesda, MD 20889, United States. Fax: +1 301 400 1307.
*E-mail address:* william.j.lowery20.mil@mail.mil (W.J. Lowery).
[1] Dr. Oliver is now affiliated with the Naval Medical Center, Portsmouth, VA.

http://dx.doi.org/10.1016/j.ygyno.2014.12.027
0090-8258/Published by Elsevier Inc.

[6]. Despite the good prognosis associated with most uterine cancers, a certain number of women will ultimately die of their disease, and it is plausible, as with other malignancies, that survival may be affected by marital status and type of relationship.

The incidence of uterine cancer rose 1% annually each of the past 10 years in the United States [7]. That rate is anticipated to increase as the largest proportion of the female population enters the age range of highest risk for this disease, and in 2014 approximately 53,000 new diagnoses and 8590 deaths are expected [8]. This is compounded by rising obesity rates in the United States, predisposing younger women to an increased risk of uterine cancer [9,10]. Despite a growing disease burden, the influence of self-reported marriage or relationship type on uterine cancer survival has not been well described. One prior large Norwegian multi-site study found no survival advantage associated with marriage among patients with uterine cancer, though overall survival was used as the endpoint rather than uterine cancer survival [11].

If uterine cancer survival varies by marital status or type of relationship, survivorship programs may have the potential to enhance patient outcomes. Understanding the impact of marriage or relationship type on uterine cancer survival and the ability to identify high-risk subpopulations can guide survivorship programs in prioritizing supportive services, personalized clinical management and care, and deployment of meaningful psychosocial interventions. Accordingly, we sought to perform a population-based study to determine whether uterine cancer survival varies by self-reported marital status or type of relationship.

## Methods

Data were downloaded from the Surveillance, Epidemiology, and End Results (SEER) program from the National Cancer Institute (NCI) for patients diagnosed in nine geographic regions (Table 1). Patients undergoing surgery for uterine cancer between 1991 and 2010 with age at diagnosis, race, ethnicity, self-reported relationship, site of disease, cell type, stage, grade, cancer survival status and cancer survival time were eligible for this project. The diagnosis of uterine cancer was based on an SEER site and histology coding for corpus uteri (C540–C543, C548–C549) and for endometrioid adenocarcinoma 8380–8383 and 8140, serous carcinoma 8460, clear cell carcinoma 8310, carcinosarcoma 8980, and other cancers 8010–8130, 8141–8263, 8320–8323, 8382–8450, 8461–8951, and 8981–9380. Patients were categorized as married, single, widow or other (divorced or separated). There were 12,208 patients that were excluded as these cases were missing data for one or more of the prognostic clinical covariates (373 were missing race, 2741 were missing type of relationship, 2034 were missing stage, 8375 were missing grade and 677 were missing adjuvant radiation status). A total of 47,420 patients met criteria for inclusion. Differences in distributions in $2 \times 2$ or in $R \times R$ contingency tables were evaluated using Chi-square, exact and/or Mantel–Haenszel test. Uterine cancer survival was analyzed by Kaplan–Meier method with log-rank test and multivariate Cox regression analysis. Statistical analysis was performed with SPSS version 20.0 (IBM Corp, Armonk, NY).

**Table 1**
Clinical characteristics of the 47,420 eligible uterine cancer patients.

| Characteristic | Cases 47,420 | % | Characteristic | Cases 47,420 | % |
|---|---|---|---|---|---|
| Age at diagnosis | | | Race | | |
| <50 | 7003 | 14.8 | Caucasian | 40,294 | 85.0 |
| 50–59 | 12,731 | 26.8 | African American | 2993 | 6.3 |
| 60–69 | 13,478 | 28.4 | Other | 4133 | 8.7 |
| 70–79 | 9825 | 20.7 | Ethnicity | | |
| 80+ | 4383 | 9.2 | Hispanic | 2151 | 4.5 |
| Year of diagnosis | | | Other | 45,269 | 95.5 |
| 1991–1995 | 11,033 | 23.3 | Historical stage | | |
| 1996–2000 | 11,921 | 25.1 | Local | 35,958 | 75.8 |
| 2001–2005 | 11,829 | 24.9 | Regional | 7816 | 16.5 |
| 2006–2010 | 12,637 | 26.6 | Distant | 3646 | 7.7 |
| Region of diagnosis | | | Histologic cell type | | |
| San Francisco/Oakland | 7730 | 16.3 | Endometrioid grade 1/2 | 31,913 | 67.3 |
| Connecticut | 7145 | 15.1 | Endometrioid grade 3 | 6369 | 13.4 |
| Metropolitan Detroit | 7292 | 15.4 | Serous | 1168 | 2.5 |
| Hawaii | 2558 | 5.4 | Clear cell | 537 | 1.1 |
| Iowa | 6924 | 14.6 | Carcinosarcoma | 442 | 0.9 |
| New Mexico | 2497 | 5.3 | Other | 6991 | 14.7 |
| Seattle/Puget Sound | 6530 | 13.8 | Radiation therapy | | |
| Utah | 3260 | 6.9 | No | 33,908 | 71.5 |
| Metropolitan Atlanta | 3483 | 7.3 | Yes | 13,512 | 28.5 |

## Results

Of the 47,420 eligible patients, 56% were married, 15% were single and 19% were widows. Table 1 indicates the characteristics for the eligible patients. The majority of patients were Caucasian race (85%), had disease localized to the uterus or adnexa (76%) and tumors with an endometrioid histology (81%). Only 29% of the patients received radiation therapy.

Married women were less likely to be African American, diagnosed at older age, have metastatic or high-risk disease, and to die of uterine cancer (Table 2, $p < 0.0001$). Married women had better uterine cancer survival than women who reported being not married (Fig. 1A, $p < 0.0001$). Subset analysis demonstrated a survival advantage of marriage in uterine cancer patients diagnosed with local disease (Fig. 1B, $p < 0.0001$) vs. metastatic disease (Fig. 1C, $p < 0.0001$) and in those who were Caucasian or other race (Fig. 1D, $p < 0.0001$) vs. African American women (Fig. 1E, $p < 0.0001$). In addition, married women had a reduced risk of cancer death, hazard ratio (HR) = 0.8, 95% confidence interval (CI) = 0.77–0.84, $p < 0.0001$, that withstood adjustments for prognostic clinical covariates including age at diagnosis, African American race, Hispanic ethnicity, stage, cell type by grade, and radiation treatment (Table 3).

Multivariate Cox modeling was then performed to determine if there was any evidence to suggest that uterine cancer survival varied among the non-married women (single vs. widow vs. other). Divorced and separated women represented about 10% of the cohort and were bundled together as their uterine cancer survival distributions were similar (Supplementary Table S1). Single women were set as the reference group in the Cox Regression analysis displayed in Table 3 under Model #2. Evaluation of uterine cancer survival by relationship type indicated that relative to single women, widows had significantly worse uterine cancer survival (HR = 1.278, 95% CI = 1.178–1.387, $p < 0.0001$), divorced and separated women had similar uterine cancer survival (HR = 1.034, 95% CI = 0.937–1.140, $p = 0.509$), and married women had slightly better uterine cancer survival (HR = 0.913, 95% CI = 0.849–0.983, $p = 0.016$). The Kaplan–Meier plot in Fig. 2 illustrates that widows had the worst uterine cancer survival and that most of the benefit previously attributed to marriage reflected the poor outcome observed in widows. Widows consistently had significantly worse uterine cancer survival than single, married and other women ($p < 0.0001$) in analyses performed in all patients (Fig. 2A, $p < 0.0001$) and the subset with local disease (Fig. 2B, $p < 0.0001$), metastatic disease (Fig. 2C, $p < 0.0001$), Caucasian or other race (Fig. 2D, $p < 0.0001$) or African American or black race (Fig. 2E, $p < 0.0001$). The differences in uterine cancer survival between single vs. married vs. other women were not dramatic (see the legend for Fig. 2 for the differences with a significant log-rank test).

Multivariate Cox modeling was then performed for women categorized as a widow (yes vs. no) with adjustments for age at diagnosis, African American race, Hispanic ethnicity, stage, cell type by grade, and radiation treatment (Table 3, Model #3). Widows had an increased risk of uterine cancer death (HR = 1.354, 95% CI = 1.280–1.433, $p < 0.0001$) relative to women with all other types of relationship (singles, married, divorced or separated). Fig. 3 illustrates the difference in the survival distribution for widowed vs. non-widowed women in an analysis involving all the patients (Fig. 3A, $p < 0.0001$), and the