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Less versus more radical surgery in stage IB1 cervical cancer: A population-based study of long-term survival

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HIGHLIGHTS

- In this study, patients with IB1 cervical cancer had 10-year DSS of 93.5% after LRS.
- There was no difference in 10-year DSS between those who underwent LRS versus MRS.
- Tumors >2 cm portend worse oncologic outcomes regardless of surgical radicality.

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ABSTRACT

Background. Standard surgical treatment for women with stage IB1 cervical cancer consists of radical hysterectomy. This study assesses survival outcomes of those treated with less radical surgery (LRS; conization, trachelectomy, simple hysterectomy) compared to more radical surgery (MRS; modified radical, radical hysterectomy).

Methods. Using the Surveillance, Epidemiology and End Results database, we identified women <45 years with FIGO stage IB1 cervical cancer diagnosed from 1/1998 to 12/2012. Only those who underwent lymph node (LN) assessment were analyzed. Disease-specific survivals (DSSs) of LRS were compared with those of MRS.

Results. Of 2571 patients, 807 underwent LRS and 1764 underwent MRS, all with LN assessment. For LRS vs. MRS, 28% vs. 23% were diagnosed with adenocarcinoma ($p = 0.024$), 31% vs. 39% had G3 disease ($p < 0.001$), 40% vs. 45% had tumor size >2 cm ($p < 0.001$), and 27% vs. 29% received adjuvant radiation therapy ($p = 0.005$). Median follow-up was 79 months (range, 0–179). Ten-year DSS for LRS vs. MRS was 93.5% vs. 92.3% ($p = 0.511$). There was no difference in 10-year DSS when stratified by tumor size ≤2 cm (LRS 95.1% vs. MRS 95.6%, $p = 0.80$) or > 2 cm (LRS 90.1% vs. MRS 88.2%, $p = 0.48$). Factors independently associated with increased risk of death included adenosquamous histology (HR 2.37), G3 disease (HR 2.86), tumors >2 cm (HR 1.82), and LN positivity (HR 2.42). Compared to MRS, LRS was not associated with a higher risk of death.

Conclusions. In a select group of young women with stage IB1 cervical cancer, LRS compared to MRS does not appear to compromise DSS.

1. Introduction

Cervical cancer is the most common gynecologic malignancy worldwide and the second leading cause of cancer death in women aged 20 to 39 [1,2]. Approximately 13,000 new cases are diagnosed annually in the United States, and nearly 40% of these diagnoses are in women younger than age 45 [1,2]. Fortunately, 80–95% of women with early-stage disease are cured by surgery [3,4].

According to the National Comprehensive Cancer Network (NCCN) guidelines, standard surgical treatment for stage IB1 carcinoma of the cervix consists of radical hysterectomy (complete removal of the uterus, cervix, upper vagina, and parametrium) and pelvic lymphadenectomy. Parametrial involvement is one of the strongest predictors of recurrence and decreased survival. Yet, only 5–30% of patients with early-stage cervical cancer are found to have parametrial involvement on final pathology [5]. Furthermore, in women with favorable risk factors such as tumor size ≤2 cm or depth of invasion <10 mm, the risk of parametrial involvement is <1% [6–9]. Tumoral excision without parametrectomy may, therefore, be adequate in a subset of early-stage cervical cancer patients. It should also be noted that radical hysterectomy carries a 10–15% risk of postoperative complications [10] with the potential for

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long-term urologic, sexual and colorectal sequelae [11–13]. For these reasons, there have been increased efforts to identify patients suited to less radical surgery (LRS) [14,15].

Most published studies regarding LRS for cervical cancer are based on small sample sizes. Early stages of disease are commonly grouped together in these studies, making it difficult to extrapolate data pertaining to one specific stage [9]. Additionally, there are few reports on LRS in patients with tumor size >2 cm. Thus, evidence to support the routine use of LRS in women with stage IB1 cervical cancer is still lacking. Our objective was to assess disease-specific survival (DSS) and other factors associated with LRS (defined as conization, trachelectomy or simple hysterectomy) compared to more radical surgery (MRS) (defined as modified radical or radical hysterectomy) in women with stage IB1 carcinoma of the cervix.

2. Methods

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, we identified all women younger than age 45 with FIGO stage IB1 squamous cell, adenocarcinoma or adenosquamous cervical cancer diagnosed between January 1998 and December 2012, who underwent surgery as primary treatment. The SEER database is a population-based cancer registry that accounts for approximately 28% of the United States population, and is thought to generally represent the U.S. demographic. For this study, we used the SEER 18 registries, which include data from 18 tumor registries located in 13 different states. Only patients who underwent LN assessment were included in the analysis. Younger patients are more likely to be treated with less radical surgery, such as conization or trachelectomy, in the interest of preserving fertility. In order to maintain a more homogeneous population, we therefore restricted our analysis to women younger than 45.

SEER registry staff are instructed to use clinical findings as the appropriate coding and staging method for cervical cancer. FIGO 2009 stage was derived from tumor location and size using the SEER Extent of Disease (EOD; 1998–2003) and Collaborative Staging codes (CS; 2004–2012). Parameters for our initial database query included carcinoma of the cervix, age < 45, diagnosis between 1998 and 2012, EOD and CS codes for stage IB disease, and surgery as primary treatment. A total of 5418 cases were identified. We arrived at our final cohort of 2571 cases after sequential exclusion of the following: stage IB2 disease (n = 735), stage IB disease not otherwise specified (NOS; n = 1018), non-squamous cell/adenocarcinoma/adenosquamous histology (n = 617), undifferentiated grade (n = 47), hysterectomy NOS as surgical procedure (n = 163), absence of regional lymph node assessment (n = 267).

We examined demographic and clinicopathologic data including age at diagnosis, race (white, black, Hispanic, other), marital status (single, married/domestic partner, divorced/widowed/separated, unknown), geographic area of residence at the time of diagnosis, year of diagnosis, histologic subtype, grade (1, 2, 3, unknown), tumor size, primary surgical treatment, performance of lymphadenectomy, LN status, and adjuvant radiation treatment (RT) (none, external beam, brachytherapy, both). Geographic area of residence was categorized as central (Detroit, Iowa, Kentucky, Louisiana, Utah), eastern (Atlanta, Connecticut, New Jersey, greater Georgia, rural Georgia), or western (Alaska, California, Hawaii, Los Angeles, New Mexico, Seattle, San Francisco/Oakland, San Jose). Year of diagnosis was stratified by 4-year intervals (1998–2002, 2003–2007, 2008–2012). Surgical procedure categories derived from SEER site-specific surgery codes included the following: cone biopsy, trachelectomy (simple versus radical not specified in the SEER database), simple hysterectomy, modified radical hysterectomy, radical hysterectomy, or modified radical/radical hysterectomy without further specification. Characteristics and disease-specific survival of those who underwent LRS were compared to those who underwent MRS.

2.1. Statistical analysis

In our comparison of demographic and clinicopathologic data, categorical variables were analyzed using the Chi-square test; median values for continuous variables were analyzed using the Mann-Whitney *U* test. Predictors of LRS versus MRS were evaluated using univariate and multivariable logistic regression models. The Kaplan-Meier method was used to estimate DSS, and survival distributions were compared with the Log-rank test. DSS was defined as the time from diagnosis to the time of disease-related death. Patients who died of non-disease-related causes, or who were alive at the time of this analysis, were censored. Median follow-up was calculated using the Kaplan-Meier estimate of potential follow-up. Factors associated with DSS were assessed using the Cox proportional hazards model. Variables with a p-value of <0.2 on univariate analysis, were subject to multivariable analysis. All variables were tested for multicollinearity. p-Values were two-tailed, and values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS for Windows, Version 24.0 (IBM Corporation, Armonk, NY).

3. Results

Among 2838 women identified, 234 of the 1041 (22.4%) who were treated with LRS, and 33 of the 1797 (1.8%) treated with MRS, did not undergo LN assessment and were therefore excluded. The final cohort comprised 2571 stage IB1 cervical cancer patients, all of whom had LN evaluation.

Of these 2571 patients, 807 (31.3%) underwent LRS (conization, n = 36; trachelectomy, n = 89; simple hysterectomy, n = 682) and 1764 (68.6%) underwent MRS (modified radical hysterectomy, n = 278; radical hysterectomy, n = 312; modified radical/radical hysterectomy, n = 1174). Demographic and clinicopathologic characteristics are shown in Table 1. Median age was 37 (range, 17–44). Most women were white (n = 1393, 54%) or Hispanic (n = 715, 28%); most were married or in a relationship with a domestic partner (n = 1388, 54%). The most common histology was squamous cell (n = 1702, 66%), followed by adenocarcinoma (n = 642, 25%). One thousand four hundred and fourteen patients (55%) had tumors ≤2 cm. LN metastasis was identified in 444 (17%) patients. Seven hundred and twenty-four (28.2%) received adjuvant RT.

Characteristics of the LRS versus MRS groups are shown in Table 2. Patients who underwent LRS were diagnosed more recently (2008–2012, 43% vs. 35%; 1998–2002, 22% vs. 30%; p < 0.001), and more commonly had tumors with adenocarcinoma histology (28% vs. 23%; p = 0.024) and a lower grade of disease (G1, 15% vs. 10%; G3, 31% vs. 39%; p < 0.001); these patients less commonly had tumors >2 cm (40% vs. 45%; p < 0.001), and less commonly received adjuvant RT (27% vs. 29%; p = 0.005). There were no significant differences in age, race, marital status, SEER region at the time of diagnosis, or rate of LN positivity.

Table 3 summarizes factors associated with surgical radicality. Patients with G3 disease were more likely to undergo MRS (adjusted OR 1.61, 95% CI 1.18–2.19), while patients with a more recent diagnosis were less likely to undergo MRS (2003–2007, adjusted OR 0.74, 95% CI 0.6–0.93; 2008–2012, adjusted OR 0.62, 95% CI 0.5–0.78). On univariate analysis, adenocarcinoma histology, G2 disease, and tumor size >2 cm, were significantly associated with MRS; however, these relationships became insignificant after adjustment for potentially confounding factors.

Median follow-up for the entire cohort was 79 months (range, 0–179), 67 months (range, 0–179 months) for the LRS group, and 84 months (range, 0–179 months) for the MRS group. On Kaplan-Meier analysis (Fig. 1A), 10-year DSS was 93.5% for women who underwent LRS versus 92.3% for those who underwent MRS (p = 0.511). When stratified by tumor size (Table 4), there was no significant difference in DSS between LRS versus MRS in the setting of tumors