Published in final edited form as:

Int J Gynecol Cancer. 2018 September ; 28(7): 1350–1359. doi:10.1097/IGC.0000000000001319.

LONG-TERM ONCOLOGIC OUTCOMES OF UTERINE-PRESERVING SURGERY IN YOUNG WOMEN WITH STAGE IB1 CERVICAL CANCER

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Abstract

Objective—To evaluate oncologic outcomes of women with stage IB1 cervical cancer treated with uterine-preserving surgery (UPS) (defined as conization or trachelectomy) vs. non-UPS (defined as hysterectomy of any type).

Methods—The Surveillance, Epidemiology, and End Results (SEER) database was used to identify women <45 years old diagnosed with stage IB1 cervical cancer from 1998-2012. Only those who underwent lymph node (LN) assessment were included. Outcomes of UPS vs. non-UPS were analyzed.

Results—Among 2717 patients, 125 were treated with UPS and 2592 were treated with non-UPS. Those in the UPS group were younger (median age 33 vs. 37 years, $p<0.001$), less commonly had tumor size >2 cm (27% vs. 45%, $p<0.001$), and less commonly received adjuvant radiation therapy (RT) (18% vs. 29%, $p=0.006$). There was no difference in distribution of tumor grade, histology, or rate of LN positivity. Median follow-up was 79 months (range, 0-179). There was no difference in 5-year disease-specific survival (DSS) between the UPS vs. non-UPS groups (93% vs. 94%, respectively, $p=0.755$). When stratified by tumor size, DSS for UPS vs. non-UPS was as follows: tumors ≤ 2 cm, 96.8% vs. 96.3% ($p=0.683$); tumors >2 cm, 82.4% vs. 90.4% ($p=0.112$). Factors independently associated with worsened survival included adenosquamous histology (HR 2.29, 95% CI 1.51-3.47), G3 disease (HR 2.44, 95% CI 1.01-5.89), tumor size >2 cm (HR 1.93, 95% CI 1.36-2.75) and LN positivity (HR 2.29, 95% CI 1.64-3.22). UPS was not associated with a higher risk of death.

Conclusions—UPS does not appear to compromise oncologic outcomes in a select group of young women with stage IB1 cervical cancer, especially in the setting of tumors ≤ 2 cm. Further studies are needed to clarify the role of UPS in tumors >2 cm.

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Disclosures: The authors declare no conflicts of interest

This study was presented in part at the 16th Biennial Meeting of the International Gynecologic Cancer Society (IGCS) in Lisbon, Portugal, October 29-31, 2016.

INTRODUCTION

Approximately 13,240 new cases of cervical cancer are diagnosed in the United States annually (1). Cervical cancer is most frequently found among women aged 35-44. Almost 40% of cases are diagnosed between the ages of 20 and 44, with disease confined to the cervix in approximately 46% of these patients (1).

Standard therapy for International Federation of Gynecology and Obstetrics (FIGO) Stage IB1 cervical cancer is radical hysterectomy with bilateral pelvic lymphadenectomy, resulting in loss of fertility. However, many women now delay childbearing. Therefore, uterine preservation is of great importance to younger women (<45 years old) diagnosed with cervical cancer.

Radical vaginal trachelectomy, as a means of uterine preservation, was first introduced by Dargent et al in 1994 (2). A variety of additional uterine-preserving surgeries (UPS) have been proposed since that time: abdominal radical trachelectomy (by laparotomy or minimally invasive approach), simple trachelectomy, and cervical conization alone (2-5). The goal of these procedures is to preserve fertility without compromising oncologic outcomes. More than two decades of accumulated data from small retrospective studies have shown that, in properly selected patients, a conservative surgical approach with radical trachelectomy is both feasible and safe (6,7). The National Comprehensive Cancer Network (NCCN) guidelines now include radical trachelectomy with either pelvic lymph node (LN) dissection or sentinel lymph node mapping as acceptable options in the management of women with FIGO Stage IB1 cervical cancer who wish to maintain reproductive function.

There has been increasing interest in further reducing the morbidities associated with radical trachelectomy, by performing simple conization alone (8,9). However, there is very limited data regarding the oncologic safety of conization alone, as the majority of published reports on fertility preservation have focused on trachelectomy for IB1 disease. Many studies on UPS are based on small sample sizes and short follow-up, making it difficult to draw generalizable conclusions for evidence-based practice. The majority of published studies also combine several FIGO stages for analysis, resulting in limited data pertaining to a single stage of disease. Additionally, tumors >2 cm are associated with higher risk of recurrence and worse overall survival (OS), and clinicians are less likely to offer uterine preservation in the setting of these larger tumors (10-13). As a result, there is little data concerning the safety of UPS in patients with larger IB1 tumors. Our primary aim was to evaluate long-term oncologic outcomes of younger women with Stage IB1 cervical cancer treated with UPS compared to those treated with non-UPS. Our secondary aim was to assess demographic and clinical factors associated UPS versus non-UPS.

METHODS

Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database were used. SEER is a national population-based cancer registry that covers approximately 28% of the United States population and comprises several geographically distinct tumor registries. The demographic characteristics of the SEER registries have been

previously described (14). The SEER 18 registries were used for this analysis, which include data from 18 geographic areas located in 13 different states.

We identified women younger than age 45, diagnosed with FIGO Stage IB1 squamous cell, adenocarcinoma or adenosquamous cervical cancer between January 1998 and December 2012, who were treated with primary surgery. Only those who underwent LN assessment were analyzed. FIGO 2009 stage was derived from SEER Extent Of Disease (EOD; 1998-2003) and Collaborative Staging codes (CS; 2004-2012). Our initial query consisted of all patients with cervical carcinoma, age < 45, EOD and CS codes for stage IB disease, diagnosis between 1998-2012, and surgery as their primary treatment. This yielded 5418 cases. After sequentially excluding those with 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), and those who did not undergo regional lymph node assessment (n=284), we arrived at our final cohort of 2717 patients.

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 (G1, G2, G3, unknown), tumor size, primary surgical treatment, performance of lymphadenectomy, LN status, and adjuvant radiation treatment (RT) (none, external beam, brachytherapy, both) were examined. SEER registry staff are instructed to code the most extensive surgery if patients have had multiple surgical procedures of the primary site. Thus, patients who underwent only a trachelectomy were coded as having had a trachelectomy, while patients who underwent a trachelectomy followed by a completion hysterectomy were coded as having had a hysterectomy. Year of diagnosis was stratified by 4-year intervals (1998-2002, 2003-2007, 2008-2012) and 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).

Analysis was based upon whether patients underwent UPS or non-UPS as their primary treatment. UPS was defined as conization alone or trachelectomy; non-UPS was defined as hysterectomy of any type (including simple hysterectomy, modified radical or radical hysterectomy, and hysterectomy not otherwise specified (NOS)). Trachelectomy was not further specified as being simple or radical in the SEER database. Characteristics and outcomes of patients treated with UPS were compared to those treated with non-UPS.

Statistical Analysis

Categorical variables were compared using the Chi-squared test. Median values for continuous variables were compared using the Mann-Whitney U test. Predictors of UPS were analyzed using univariate and multivariable logistic regression models. The Kaplan-Meier method was used to estimate disease-specific survival (DSS), and survival distributions were compared using the Log-rank test. DSS was defined as the time from date of diagnosis to date of death due to disease. Patients who were deceased from non-disease-

related causes, or alive at the time of analysis, were censored. Median follow-up time was calculated using the Kaplan-Meier estimate of potential follow-up. Factors associated with DSS were evaluated using the Cox proportional hazards model.

Clinically significant variables and variables with a p-value <0.2 on univariate analysis were included in a multivariable analysis. All variables were tested for multicollinearity. Calculated p-values were two-tailed, and p-values <0.05 were considered significant. Statistical analyses were performed using IBM SPSS for Windows, version 24.0 (IBM Corporation, Armonk, NY).

RESULTS

A total of 3001 Stage IB1 cervical cancer patients were identified: 197 who underwent UPS and 2804 who underwent non-UPS. Only those who had LN evaluation (125/197 (64%) in the UPS group; 2592/2804 (92%) in the non-UPS group) were included in our final cohort of 2717 patients.

Demographic and clinicopathologic data are summarized in Table 1. Median age overall was 37 years (range, 17-44). Most patients were either married or in a relationship with a domestic partner (n=1470, 54%). The most common histology was squamous cell (n=1804, 66%); 1477 (54%) of tumors were ≤ 2 cm. Four hundred and sixty-six patients (17%) had positive LNs. Seven hundred and seventy patients (28%) received adjuvant RT.

Among these 2717 patients, 125 underwent UPS with conization (n=36) or trachelectomy (n=89). The remaining 2592 patients underwent non-UPS with either simple hysterectomy (n=682), modified radical/radical hysterectomy (n=1764), or hysterectomy NOS (n=146). Table 2 summarizes the demographic and clinicopathologic characteristics of those treated with UPS versus non-UPS. Patients in the UPS group were younger (median age 33 vs. 37 years), were more often diagnosed between 2008 and 2012 (55% vs. 36%), more commonly presented with tumor size ≤ 2 cm (70% vs. 54%), and less commonly received adjuvant RT (18% vs. 29%). There were no significant differences in race, marital status, SEER region, histology, grade, or LN positivity between the groups.

Factors associated with UPS are shown in Table 3. UPS was associated with younger patients (adjusted OR for age 0.88, 95% CI 0.85-0.91), and those diagnosed between 2008 and 2012, compared to earlier dates (adjusted OR 3.77, 95% CI 2.11-6.75). In contrast, UPS was less frequently associated with tumors >2 cm (adjusted OR 0.48, 95% CI 0.31-0.73). These were independently associated after adjusting for potentially confounding factors.

Median follow-up for the entire cohort was 79 months (range, 0-179). DSS data are summarized in Table 4. As depicted by the Kaplan Meier curves (Figure 1A), there was no significant difference in 5-year DSS between the two groups (92.9% vs. 93.7% for UPS and non-UPS, respectively (p=0.755)). One thousand four hundred and seventy-seven women had tumors ≤ 2 cm; 1197 had tumors >2 cm. Of those with tumors ≤ 2 cm, 87 underwent UPS (conization n=19, trachelectomy n=68) and 1390 underwent non-UPS (simple hysterectomy n=387, modified radical/radical hysterectomy n=949, hysterectomy NOS n=63). Of those with tumors >2 cm, 34 underwent UPS (conization n=16, trachelectomy n=18) and 1163

underwent non-UPS (simple hysterectomy n=285, modified radical/radical hysterectomy n=797, hysterectomy NOS n=81). Five-year DSS for those with tumors ≤ 2 cm was 96.8% for the UPS group, versus 96.3% for the non-UPS group ($P=0.683$; Figure 1B). There was no statistically significant difference in 5-year DSS for patients with tumors >2 cm (DSS 82.4% for the UPS group vs. 90.4% for the non-UPS group, $p=0.112$; Figure 1C). However, when comparing survival between all patients with tumors ≤ 2 cm to those with tumors >2 cm, regardless of UPS or non-UPS, patients with larger tumors had significantly worse 5-year DSS (tumor <2 cm 96.3% vs. tumor >2 cm 90.2%, $p<0.001$; Figure 1D). Patients with negative LNs had improved 5-year DSS compared to those with positive LNs (95.3% vs. 85.5%, $p<0.001$), and patients who did not receive adjuvant RT had improved survival compared to those who did receive adjuvant RT (96% vs. 87.8%, $p<0.001$).

We examined the long-term outcomes of women in whom reproductive function was truly preserved, defined as not requiring adjuvant RT after UPS. We found no significant difference in 5-year DSS between UPS (n=103) and non-UPS (n=1844) in patients who did not receive adjuvant RT (DSS was 94.8% for the UPS cohort vs. 96.0% for the non-UPS cohort, $p=0.616$; Figure 1E). Among patients with tumors ≤ 2 cm who underwent UPS, 90.8% did not receive adjuvant RT. In comparison, 41.2% of patients with tumors >2 cm who underwent UPS received adjuvant RT; thus, only 58.8% had true uterine-preserving treatment.

We analyzed the survival of patients who underwent conization alone (n=36) compared to trachelectomy (n=89). Five-year DSS for the conization group was 90%, compared to 94.1% for the trachelectomy group ($P=0.43$). However, 72.7% of patients undergoing conization received adjuvant RT, while only 27.3% undergoing trachelectomy received adjuvant RT. When analyzing only those patients who did not receive adjuvant RT, there was no significant difference in 5-year DSS (conization 100% vs. trachelectomy 93.6%, $P=0.33$).

Table 5 summarizes the association of various factors with DSS. Factors associated with disease-related death on multivariable analysis included adenosquamous histology (adjusted HR 2.29, 95% CI 1.51-3.47), G3 disease (adjusted HR 2.44, 95% CI 1.01-5.89), tumor size >2 cm (adjusted HR 1.93, 95% CI 1.35-2.75), and LN positivity (adjusted HR 2.29, 95% CI 1.64-3.22). UPS was not associated with DSS. Of note, the use of adjuvant RT was not included in this Cox proportional hazards model, due to multicollinearity with LN status. However, on a separate multivariable analysis model that did not include LN status, the use of adjuvant RT was significantly associated with an increased risk of disease-related death (adjusted HR 2.24, 95% CI 1.60-3.13).

DISCUSSION

Uterine preservation has become an increasingly significant issue among young cancer patients, especially because many women now delay childbearing. For many female cancer survivors, the negative psychosocial impact due to loss of fertility persists years after diagnosis (15,16). The majority of cervical cancer patients aged younger than 45 are found to have Stage I disease, which is associated with excellent survival (17). Preserving both fertility and a sense of normalcy after oncologic treatment is critical for these women.

In the current study, UPS resulted in excellent DSS in patients with Stage IB1 cervical cancer, similar to those who did not undergo UPS. This is likely one of the largest studies reported for this cohort, and presents the longest follow-up. Long-term follow-up has also been reported in another study with a much smaller sample size of 40 patients undergoing radical trachelectomy versus 110 patients undergoing non-UPS, which demonstrated no statistically significant difference in 5-year DSS between the two groups (92% vs. 91%) (18). These findings are comparable to ours. We report a 5-year DSS of 92.9% vs. 93.7% for UPS vs. non-UPS, respectively; these are similar to the outcomes reported for radical hysterectomy with pelvic LN dissection in early-stage disease, for which the 5-year OS ranges from 73-98% (19–23). Recurrence and mortality rates of 2-5% and 1-2%, respectively, have also been reported in carefully selected patients with early-stage disease undergoing trachelectomy (24–27).

Radical trachelectomy is considered the mainstay of UPS for Stage IB1 cervical cancer. However, conization has emerged as a potential alternative to trachelectomy in select cases (28). In the current study, we analyzed 36 Stage IB1 patients who underwent conization. Our results demonstrated no significant difference in DSS between patients undergoing conization compared to trachelectomy, with 5-year DSS of 90% and 94%, respectively. In a recent meta-analysis of patients with Stage IB1 cervical cancer, including 167 conization and 148 trachelectomies, the recurrence rate was 2% for conization and 2.3% for trachelectomy (29). However, survival data were not reported in this meta-analysis. One limitation of our analysis is that we do not know which criteria were used to decide whether patients should ultimately receive conization or trachelectomy. However, prognostic factors that can be established preoperatively, such as tumor size and lymphovascular space invasion (LVSI), were likely considered.

We noted an association between adenosquamous histology and worsened DSS. However, only 8 of the 239 adenosquamous cases underwent UPS, making it impossible to draw any conclusion regarding UPS in the setting of this specific histology.

Tumor size is recognized as an important prognostic factor in cervical cancer (30–32). UPS has typically been reserved for smaller tumors (< 2 cm in diameter) (11–13). Tumors >2 cm are associated with a higher rate of recurrence in general (3% for lesions < 2 cm vs. 17 % for lesions >2 cm) (10) and worse OS. There are limited data regarding UPS in IB1 disease with tumors >2 cm. In our analysis of tumors >2 cm, there was no statistically significant difference in DSS between the UPS and non-UPS groups (82.4% vs. 90.4%, respectively, $p=0.112$). However, there is a distinct separation of the two survival curves (Figure 1C). This may reflect worse DSS in the UPS group that was not statistically detectable due to sample size, or there may truly be no significant difference in DSS. These results must therefore be interpreted with caution.

It is important to note that, among the patients with tumors >2 cm who underwent UPS, 41.2% received adjuvant RT; thus, only 58.8% had true fertility-preserving treatment (compared to 90.8% of patients with tumors < 2 cm). Furthermore, regardless of the type of surgical approach, patients with larger tumors had significantly worse 5-year DSS (96.3% for tumor size < 2 cm vs. 90.2% for tumor size >2 cm).

LN assessment is an important factor in triaging patients to appropriate postoperative management. In this study, 91% of all Stage IB1 patients underwent LN examination, yet only 64% of those treated with UPS had LN assessment. LN involvement is one of the most significant prognostic factors, and the risk of metastasis in Stage IB1 cervical cancer is 15% (33). It is imperative that patients undergo complete surgical staging, including LN evaluation either by lymphadenectomy or sentinel LN biopsy, especially if UPS is considered.

When counseling patients about fertility-preserving options, it is crucial to discuss reproductive outcomes. These tend to be slightly different depending on the type of procedure performed, but are generally quite promising. Unfortunately, the SEER database does not collect information on obstetrical outcomes for women with early-stage cervical cancer who undergo successful UPS. In the published literature, fertility rates (20-74%) and prematurity rates (5-57%) vary widely; however, spontaneous abortion rates (15-24%) are similar to those in the general public. Live birth rates are favorable, ranging from 67-78%, (29,34–36).

The current study has several limitations, including its retrospective nature, lack of central pathology review, lack of certain pathologic data such as depth of invasion, LVSI and margin status, and absence of data on reproductive outcomes and disease recurrence. The selection criteria for UPS or adjuvant RT were not documented. Thus, there was likely a selection bias for patients who underwent UPS. Nevertheless, this study encompasses a large patient population, provides important information on long-term oncologic outcomes, and has robust external validity. It would be very difficult to perform a randomized controlled trial of cervical cancer patients wishing to preserve reproductive function, because women desiring future fertility would probably be unwilling to risk randomization to the non-UPS arm. Large retrospective studies such as ours are, therefore, of high value. There are currently 3 prospective trials (SHAPE trial, GOG 278, and the LESER trial) recruiting to evaluate quality of life and oncologic outcomes in women with early stage cervical cancer undergoing less versus more radical surgery. Although only one trial (GOG 278) offers a fertility-sparing option, these studies may present some important insights into the radicality necessary for the treatment of early stage cervical carcinoma.

In conclusion, UPS does not appear to compromise DSS in properly selected young women with Stage IB1 cervical cancer. UPS in tumors >2 cm should be performed with caution, and only in carefully selected patients, until additional studies clarify the role of uterine preservation in the setting of these larger tumors. Conization alone appears to be feasible and safe in properly selected patients with favorable risk factors. Young women with Stage IB1 cervical cancer who desire fertility preservation should be extensively counseled, and LN assessment (which should be performed in all surgical patients) is mandatory in those being considered for UPS. Ongoing studies involving the use of neoadjuvant chemotherapy followed by conization or trachelectomy may offer women with early-stage disease and poor prognostic factors, including large tumor size, the option of uterine preservation, without compromising oncologic outcomes.

Acknowledgments

Funding/Research support: This study was funded in part through the NIH/NCI Support Grant P30 CA008748

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Figure 1.

Five-year disease-specific survival for (A) Uterine-preserving surgery (UPS) vs. non-UPS; (B) UPS vs. non-UPS in the setting of tumors ≤ 2 cm; (C) UPS vs. non-UPS in the setting of tumors > 2 cm; (D) patients with tumor size ≤ 2 cm vs. > 2 cm, regardless of UPS; (E) UPS vs. non-UPS in patients who did not receive adjuvant radiotherapy.

Table 1

Demographic and clinicopathologic characteristics

Variable	Total cohort (n=2717)	
	n	(%)
Median age	37	(17-44) *
Race		
White	1466	54.0
Black	243	8.9
Hispanic	756	27.8
Other	252	9.2
Marital status		
Single	830	30.5
Married/Domestic partner	1470	54.1
Divorced/Widowed/Separated	327	12.0
Unknown	90	3.3
SEER Region		
Central	507	18.7
Eastern	543	20.0
Western	1667	61.4
Year of diagnosis		
1998-2002	735	27.1
2003-2007	977	36.0
2008-2012	1005	37.0
Histology		
Squamous cell	1804	66.4
Adenocarcinoma	674	24.8
Adenosquamous	239	8.8
Grade		
G1	299	11.0
G2	1187	43.7
G3	1000	36.8
Unknown	231	8.5
Tumor size		
2 cm	1477	54.4
> 2 cm	1197	44.1
Unknown	43	1.6
Positive LN		
No	2251	82.8

Variable	Total cohort (n=2717)	
	n	(%)
Yes	466	17.2
RT		
No	1947	71.7
Yes	770	28.3
RT type		
None	1947	71.7
External beam	534	19.7
Brachytherapy	32	1.2
Both	199	7.3
RT NOS	5	0.2

LN, lymph node; RT, radiation therapy; NOS, not otherwise specified

* Range (min-max)

Table 2
Comparison of demographic and clinical variables for UPS vs. non-UPS groups

Variable	UPS (n=125)		Non-UPS (n=2592)		P value
	n	(%)	n	(%)	
Uterine-preserving surgery					–
Conization	36	28.8	682	26.3	
Trachelectomy	89	71.2	1174	45.3	
Non-Uterine-preserving surgery					
Simple hysterectomy			278	10.7	
Modified radical/Radical hysterectomy			312	12.0	
Modified radical hysterectomy			146	5.6	
Radical hysterectomy					
Hysterectomy NOS					
Median age	33	(19–44)	37	(17–44)	<.001
Race					.670
White	73	58.4	1393	53.7	
Black	9	7.2	234	9.0	
Hispanic	34	27.2	722	27.9	
Other	9	7.2	243	9.4	
Marital status					0.05
Single	49	39.2	781	30.1	
Married/Domestic partner	55	44.0	1415	54.6	
Divorced/Widowed/Separated	14	11.2	313	12.1	
Unknown	7	5.6	83	3.2	
SEER Region					.619
Central	21	16.8	486	18.8	
Eastern	29	23.2	514	19.8	
Western	75	60.0	1592	61.4	

Variable	UPS (n=125)		Non-UPS (n=2592)		P value
	n	(%)	n	(%)	
Year of diagnosis					<.001
1998-2002	15	12.0	720	27.8	
2003-2007	41	32.8	936	36.1	
2008-2012	69	55.2	936	36.1	
Histology					.258
Squamous cell	79	63.2	1725	66.6	
Adenocarcinoma	38	30.4	636	24.5	
Adenosquamous	8	6.4	231	8.9	
Grade					.099
G1	19	15.2	280	10.8	
G2	55	44.0	1132	43.7	
G3	36	28.8	964	37.2	
Unknown	15	12.0	216	8.3	
Tumor size					<.001
2 cm	87	69.6	1390	53.6	
> 2 cm	34	27.2	1163	44.9	
Unknown	4	3.2	39	1.5	
Positive LN					.687
No	107	85.6	2144	82.7	
Yes	18	14.4	448	17.3	
RT					.006
No	103	82.4	1844	71.1	
Yes	22	17.6	748	28.9	
RT type					.055
None	103	82.4	1844	71.1	
External beam	12	9.6	522	20.1	
Brachytherapy	1	0.8	31	1.2	

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Variable	UPS (n=125)		Non-UPS (n=2592)		P value
	n	(%)	n	(%)	
Both	9	7.2	190	7.3	
RT NOS	0	0.0	5	0.2	

UPS, Uterine-preserving surgery; NOS, not otherwise specified; LN, lymph node; RT, radiation therapy

Table 3

Factors predictive of uterine-preserving surgery

Variable	Univariate		Multivariable	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Median age	0.89 (0.86 – 0.92)	<.001	0.88 (0.85 – 0.91)	<.001
Race				
White	Referent	–	–	–
Black	0.73 (0.36 – 1.49)	.391		
Hispanic	0.90 (0.59 – 1.36)	.615		
Other	0.71 (0.35 – 1.43)	.335		
Marital status				
Single	Referent	–	Referent	–
Married/Domestic partner	0.62 (0.42 – 0.92)	.017	0.77 (0.51 – 1.17)	.217
Divorced/Widowed/Separated	0.71 (0.39 – 1.31)	.276	1.06 (0.56 – 2.00)	.853
Unknown	1.34 (0.59 – 3.06)	.481	1.46 (0.62 – 3.46)	.388
SEER Region				
Central	Referent	–	–	–
Eastern	1.31 (0.74 – 2.32)	.363		
Western	1.09 (0.67 – 1.79)	.732		
Year of diagnosis				
1998-2002	Referent	–	Referent	–
2003-2007	2.10 (1.16 – 3.83)	.015	2.17 (1.18 – 3.99)	.013
2008-2012	3.54 (2.01 – 6.24)	<.001	3.77 (2.11 – 6.75)	<.001
Histology				
Squamous cell	Referent	–	Referent	–
Adenocarcinoma	1.31 (0.88 – 1.94)	.190	1.22 (0.78 – 1.91)	.387
Adenosquamous	0.76 (0.36 – 1.59)	.459	0.96 (0.45 – 2.06)	.925
Grade				
G1	Referent	–	Referent	–
G2	0.98 (0.49 – 1.97)	.948	0.77 (0.43 – 1.39)	.385
G3	0.70 (0.39 – 1.26)	.235	0.62 (0.32 – 1.18)	.145
Unknown	0.54 (0.29 – 1.00)	.050	0.98 (0.46 – 2.06)	.954
Tumor size				
2 cm	Referent	–	Referent	–
> 2 cm	0.47 (0.31 – 0.70)	<.001	0.48 (0.31 – 0.73)	.001
Unknown	1.64 (0.54 – 4.7)	.357	0.89 (0.30 – 2.67)	.840

OR, odds ratio

Table 4

Five-year disease-specific survival

	5-year DSS	SE	P value
Entire cohort			
UPS	92.9	2.6	.755
Non-UPS	93.7	0.5	
Tumor size ≤ 2 cm			
UPS	96.8	2.3	.683
Non-UPS	96.3	0.6	
Tumor size > 2 cm			
UPS	82.4	7.2	.112
Non-UPS	90.4	1.0	
Entire cohort			
Tumor size ≤ 2 cm	96.3	0.6	<.001
Tumor size > 2 cm	90.2	1.0	
Entire cohort			
Negative LN	95.3	0.5	<.001
Positive LN	85.5	1.8	
Entire cohort			
Without RT	96.0	0.5	<.001
With RT	87.8	1.3	
Without adjuvant RT			
UPS	94.8	2.6	.616
Non-UPS	96.0	0.5	

UPS, uterine-preserving surgery; RT, radiation therapy; SE, standard error; DSS, disease-specific survival

Table 5

Factors associated with disease-specific survival

Variable	Univariate		Multivariable	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Median age	0.97 (0.95 – 1.00)	.073		
Race				
White	Referent	–	–	–
Black	1.43 (0.85 – 2.39)	.174	1.28 (0.76 – 2.16)	.361
Hispanic	1.27 (0.88 – 1.82)	.200	1.20 (0.81 – 1.78)	.356
Other	1.32 (0.77 – 2.27)	.313	1.18 (0.67 – 2.08)	.561
Marital status				
Single	Referent	–	–	–
Married/Domestic partner	0.89 (0.62 – 1.27)	.511		
Divorced/Widowed/Separated	1.16 (0.71 – 1.89)	.549		
Unknown	0.85 (0.31 – 2.36)	.755		
SEER Region				
Central	Referent	–	Referent	–
Eastern	1.53 (0.91 – 2.55)	.107	1.46 (0.87 – 2.46)	0.149
Western	1.23 (0.79 – 1.92)	.365	1.06 (0.65 – 1.73)	0.807
Year of diagnosis				
1998-2002	Referent	–	Referent	–
2003-2007	0.87 (0.62 – 1.22)	.417		
2008-2012	0.67 (0.41 – 1.09)	.109		
Histology				
Squamous cell	Referent	–	Referent	–
Adenocarcinoma	0.67 (0.43 – 1.04)	.076	0.97 (0.61 – 1.56)	.908
Adenosquamous	2.35 (1.56 – 3.52)	<.001	2.29 (1.51 – 3.47)	<.001
Grade				
G1	Referent	–	Referent	–
G2	2.17 (0.93 – 5.04)	.072	1.57 (0.65 – 3.77)	.317
G3	4.13 (1.81 – 9.44)	.001	2.44 (1.01 – 5.89)	.048
Unknown	1.49 (0.52 – 4.30)	.458	1.29 (0.44 – 3.81)	.644
Tumor size				
2 cm	Referent	–	Referent	–
> 2 cm	2.66 (1.91 – 3.72)	<.001	1.93 (1.35 – 2.75)	<.001
Unknown	NE	.961	NE	.961
Surgery				
Uterine-preserving	Referent	–	Referent	–

Variable	Univariate		Multivariable	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Non-Uterine-preserving	0.89 (0.42 – 1.89)	.755	0.68 (0.32 – 1.47)	.625
Positive LN				
No	Referent	–	Referent	–
Yes	2.89 (2.09 – 4.00)	<.001	2.29 (1.64 – 3.22)	<.001
Unknown if examined	NE	.957	NE	0.99
* RT				
No	Referent	–	–	–
Yes	3.02 (2.21 – 4.13)	<.001		

HR, hazard ratio; LN, lymph node; RT, radiation therapy, NOS, not otherwise specified; NE, not estimable

* Not included in multivariable analysis due to multicollinearity