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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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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

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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.

Keywords

Cervical cancer; Simple hysterectomy; Conization; Trachelectomy; Radical hysterectomy; Disease-specific survival

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 less than 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 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.

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 1998–2012, 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.

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).

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 (Figure 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 ≤ 2 cm (Figure 1B; 10-year DSS of 95.1% vs. 95.6% for LRS vs. MRS, respectively ($p=0.799$)) or tumors >2 cm (Figure 1C; 10-year DSS of 90.1% vs. 88.2% for LRS vs. MRS, respectively ($p=0.48$)).

Factors associated with DSS are presented in Table 5. On multivariable analysis, factors significantly associated with disease-related death included adenosquamous histology (adjusted HR 2.37, 95% CI 1.55–3.63), G3 disease (adjusted HR 2.86, 95% CI 1.11–7.51), tumor size >2 cm (adjusted HR 1.82, 95% CI 1.26–2.62), and LN positivity (adjusted HR 2.42, 95% CI 1.70–3.42). Adjuvant RT was not included in this multivariable analysis due to multicollinearity with LN status. However, in a separate multivariable logistic regression model excluding LN status, treatment with adjuvant RT was significantly associated with disease-related death (adjusted HR 2.29, 95% CI 1.61–3.24).

We also analyzed DSS for patients who did not receive postoperative RT. A total of 1847 women were identified: 590 of these patients underwent LRS (conization, $n=20$; trachelectomy, $n=83$; simple hysterectomy, $n=487$) and 1257 underwent MRS (modified radical hysterectomy, $n=198$; radical hysterectomy, $n=233$; modified radical/radical hysterectomy, $n=826$). The 10-year DSS was 95.8% and 94.8% for LRS and MRS, respectively, with no statistically significant difference between the groups ($p=0.467$; Figure 1D).

DISCUSSION

For decades, the primary surgical treatment of stage IB1 cervical cancer has emphasized radicality with curative intent. Radical hysterectomies, however, are associated with increased potential for short- and long-term morbidity. The ureters, and nerve plexuses innervating the bowel and bladder, travel in close proximity to the parametria, putting urinary, sexual and anorectal function at risk during radical resection. The rate of parametrial involvement in early-stage disease ranges from $<1\%$ to 10% [6,8,16–19,31]. In patients with negative LNs, no lymphovascular space invasion (LVSI), tumor size ≤ 2 cm, and depth of invasion <10 mm, the incidence of parametrial spread is $0\text{--}0.6\%$ [4–9,16]. One study of stage IB1 patients undergoing radical hysterectomy demonstrated 0% parametrial involvement among those who were younger than age 50, with depth of invasion ≤ 10 mm and no LVSI [31]. Therefore, many have advocated for LRS (such as simple hysterectomy) as an alternative to radical hysterectomy in patients with early-stage disease and favorable risk factors [6,7,14–17,20,21].

The current study is one of the largest to date. We found that DSS for women treated with LRS is excellent, with no difference in survival between LRS and MRS groups (93.5% vs. 92.3%, respectively). Our results are comparable to those of a randomized controlled trial of simple versus radical hysterectomy for stage IB1-IIA cervical cancer patients, which

reported no significant difference in 5-year overall survival between the two groups and less morbidity in the simple hysterectomy group [22]. With respect to 5-year overall survival following surgical treatment of early-stage disease, our results are also similar to those in the literature—the reported rates ranging from 89–98% [23–27].

In this study, adenosquamous histology was significantly associated with poorer DSS. Assessment of the prognostic significance of adenosquamous cervical cancer in the literature has been limited because it is a relatively rare pathologic entity, and is often included as a subtype of adenocarcinoma. Here, we report on a large cohort of 227 patients with adenosquamous cervical cancer, of whom 65 underwent LRS and 162 MRS. Our findings are consistent with those reported in a recent review and meta-analysis indicating that adenosquamous tumors portend poorer recurrence-free and overall survival compared with cervical adenocarcinomas [28].

Tumors >2 cm are known to be associated with a higher rate of recurrence (5% for lesions ≤2 cm vs. 13% for lesions >2 cm) [29] and worse overall survival [8,19]. Thus, a majority of the literature on LRS for cervical cancer has focused on tumors ≤2 cm. We stratified our cohort according to tumor diameter (≤ or > 2 cm) and identified 1116 women with tumors >2 cm, 391 of whom underwent LRS. Our results show no difference in DSS between the LRS and MRS groups (10-year DSS, 90.3% and 88.9% for LRS and MRS, respectively). Regardless of the type of surgical approach, however, patients with tumors measuring >2 cm had significantly worse 10-year DSS than patients with tumors measuring ≤2 cm (95.4% for tumor size ≤2 cm vs. 88.9% for tumor size >2 cm).

It is important to note that, among the entire cohort, only 77.5% of those treated with LRS underwent LN assessment. This is inadequate and unacceptable. The rate of LN metastasis in stage IB1 cervical cancer is approximately 15% [30], and LN status is one of the most important prognostic indicators in cervical cancer. It is imperative that *all* patients with stage IB1 disease undergo LN evaluation, so that they can be adequately counseled, and appropriately triaged for adjuvant treatment. To maintain a homogeneous patient population, we restricted our analysis to those who underwent regional LN assessment.

The current study is limited by its retrospective nature, non-centralized pathology review, lack of some pathologic data such as depth of invasion, LVSI and margin status, an absence of data regarding disease recurrence, and possible inaccuracy of radiotherapy data reporting. As well, this study lacks documentation of the criteria used to select patients for LRS versus MRS. Therefore, we must note that the outcomes of those treated with LRS may be representative of a select cohort with favorable risk factors. However, this is one of the largest studies to address long-term oncologic outcomes in IB1 cervical cancer patients undergoing LRS, especially in the setting of tumors >2 cm. Furthermore, our use of the SEER database provides robust external validity.

In conclusion, treatment with conization, trachelectomy, or simple hysterectomy does not appear to compromise long-term oncologic outcomes in women with stage IB1 cervical cancer. Patient selection may play a vital role in determining outcomes for those treated with LRS. Patients with tumors >2 cm undergoing LRS appear to have survival outcomes

equivalent to those of patients undergoing MRS, although patients with tumors >2 cm are more likely to require adjuvant treatment, and may have worse oncologic outcomes regardless of surgical radicality. When considering LRS, prognostic factors—including depth of invasion, LVSI, tumor size, histology, and the risk of nodal spread and parametrial involvement—should always be evaluated carefully. Currently there are three prospective trials (ConCerv, SHAPE, and GOG-278) recruiting low-risk, early-stage cervical cancer patients for the assessment of oncologic outcomes after LRS. As we await the results of these prospective trials, our large population study may be of great value in guiding the decision-making process for radicality of surgical treatment in patients with stage IB1 cervical cancer.

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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

Figure 1. 10-year DSS for (A) LRS vs. MRS, (B) LRS vs. MRS in patients with tumors ≤ 2 cm, (C) LRS vs. MRS in patients with tumors > 2 cm, (D) LRS vs. MRS in patients who did not receive adjuvant RT.

Abbreviations: DSS, disease-specific survival; LRS, less radical surgery; MRS, more radical surgery; RT, radiotherapy.

Table 1.

Demographic and clinicopathologic characteristic

Variable	Total cohort (n=2571)	
	n	(%)
Median age	37	(17–44) ^a
Race		
White	1393	54.2
Black	224	8.7
Hispanic	715	27.8
Other	239	9.3
Marital status		
Single	788	30.6
Married/Domestic partner	1388	54.0
Divorced/Widowed/Separated	311	12.1
Unknown	84	3.3
SEER Region		
Central	485	18.9
Eastern	483	18.8
Western	1603	62.3
Year of diagnosis		
1998–2002	702	27.3
2003–2007	911	35.4
2008–2012	958	37.3
Histology		
Squamous cell	1702	66.2
Adenocarcinoma	642	25.0
Adenosquamous	227	8.8
Grade		
G1	292	11.4
G2	1128	43.9
G3	929	36.1
Unknown	222	8.6
Tumor size		
2 cm	1414	55.0
> 2 cm	1116	43.4
Unknown	41	1.6
Positive LN		
No	2126	82.7
Yes	444	17.3
Unknown if examined	1	0.0
RT		
No	1847	71.8

Variable	Total cohort (n=2571)	
	n	(%)
Yes	724	28.2
RT type		
None	1847	71.8
External beam	508	19.8
Brachytherapy	28	1.1
Both	183	7.1
RT NOS	5	0.2

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

^aRange (min-max)

Table 2.

Comparison of demographic and clinicopathologic variables for LRS vs MRS groups

Variable	Less radical (N=807)		More radical (N=1764)		<i>p</i> value
	<i>N</i>	(%)	<i>N</i>	(%)	
Less radical surgery					--
Conization	36	4.5			
Trachelectomy	89	11.0			
Simple hysterectomy	682	84.5			
More radical surgery					
Modified radical/Radical hysterectomy			1174	66.6	
Modified radical hysterectomy			278	15.8	
Radical hysterectomy			312	17.7	
Median age	37	(18–44)	37	(17–44)	.834
Race					.857
White	482	53.0	965	54.7	
Black	74	9.2	150	8.5	
Hispanic	230	28.5	485	27.5	
Other	75	9.3	164	9.3	
Marital status					.939
Single	246	30.5	542	30.7	
Married/Domestic partner	434	53.8	954	54.1	
Divorced/Widowed/Separated	98	12.1	213	12.1	
Unknown	29	3.6	55	3.1	
SEER Region					.219
Central	137	17.0	348	19.7	
Eastern	160	19.8	323	18.3	
Western	510	63.2	1093	62.0	
Year of diagnosis					<.001
1998–2002	176	21.8	562	29.8	
2003–2007	283	35.1	628	35.6	
2008–2012	348	43.1	610	34.6	
Histology					.024
Squamous cell	513	63.6	1189	67.4	
Adenocarcinoma	229	28.4	413	23.4	
Adenosquamous	65	8.1	162	9.2	
Grade					<.001
G1	117	14.5	175	9.9	
G2	362	44.9	766	43.4	
G3	249	30.9	680	38.5	
Unknown	79	9.8	143	8.1	
Tumor size					<.001
2 cm	465	57.6	949	53.8	

Variable	Less radical (N=807)		More radical (N=1764)		<i>p</i> value
	<i>N</i>	(%)	<i>N</i>	(%)	
> 2 cm	319	39.5	797	45.2	
Unknown	23	2.9	18	1.0	
Positive LN					.214
No	6382	84.5	1444	81.9	
Yes	125	15.5	319	18.1	
Unknown if examined	0	0.0	1	0.1	
RT					.005
No	590	73.1	1257	71.3	
Yes	217	26.9	507	28.7	
RT type					.716
None	590	73.1	1257	71.3	
External beam	147	18.2	361	20.5	
Brachytherapy	10	1.2	18	1.0	
Both	58	7.2	125	7.1	
RT NOS	2	0.2	3	0.2	

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

Table 3.

Factors predictive of more radical surgery

Variable	Univariate		Multivariable	
	OR (95% CI)	<i>p</i> value	Adjusted OR (95% CI)	<i>p</i> value
Median age	1.00 (0.98 – 1.02)	.881		
Race				
White	Referent	--	--	--
Black	0.90 (0.67 – 1.222)	.488		
Hispanic	0.94 (0.77 – 1.14)	.499		
Other	0.97 (0.72 – 1.30)	.893		
Marital status				
Single	Referent	--	--	--
Married/Domestic partner	1.00 (0.83 – 1.21)	.981		
Divorced/Widowed/Separated	0.97 (.74 – 1.31)	.925		
Unknown	0.96 (0.54 – 1.38)	.536		
SEER Region				
Central	Referent	--	--	--
Eastern	0.80 (0.60 – 1.05)	.795		
Western	0.84 (0.67 – 1.06)	.844		
Year of diagnosis				
1998–2002	Referent	--	Referent	--
2003–2007	0.74 (0.60 – 0.93)	.008	0.74 (0.60 – 0.93)	.009
2008–2012	0.59 (0.47 – 0.73)	<.001	0.62 (0.50 – 0.78)	<.001
Histology				
Squamous cell	Referent	--	Referent	--
Adenocarcinoma	0.78 (0.64 – 0.94)	.010	0.94 (0.76 – 1.17)	.576
Adenosquamous	1.08 (0.79 – 1.46)	.641	1.05 (0.77 – 1.42)	.781
Grade				
G1	Referent	--	Referent	--
G2	1.42 (1.09 – 1.85)	.010	1.31 (0.98 – 1.74)	.069
G3	1.83 (1.39 – 2.41)	<.001	1.61 (1.18 – 2.19)	.003
Unknown	1.21 (0.84 – 1.74)	.0300	1.12 (0.77 – 1.63)	.556
Tumor size				
2 cm	Referent	--	Referent	--
> 2 cm	1.22 (1.03 – 1.45)	.020	1.15 (0.96 – 1.37)	.128
Unknown	0.34 (0.21 – 0.72)	.003	0.47 (0.25 – 0.89)	.020

Abbreviations: OR, odds ratio

Table 4.

Disease-specific survival stratified by tumor size

	Tumor diameter ≤ 2 cm				Tumor diameter > 2 cm			
	LRS	SE	MRS	SE	LRS	SE	MRS	SE
5-year DSS	96.6%	0.9	96.3%	0.7	90.1%	1.8	90.1%	1.2
10-year DSS	95.1%	1.3	95.6%	0.8	90.1%	1.8	88.2%	1.3
P-value, 10-year DSS	.799				.480			
P-value, 10-year DSS					<.001			

Abbreviations: LRS, less radical surgery; MRS, more radical surgery; 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	0.98 (0.95 – 1.01)	.162		
Race				
White	Referent	--	--	--
Black	1.52 (0.90 – 2.59)	.121		
Hispanic	1.23 (0.84 – 1.81)	.279		
Other	1.35 (0.77 – 2.36)	.295		
Histology				
Squamous cell	Referent	--	Referent	--
Adenocarcinoma	0.70 (0.45 – 1.11)	.132	1.02 (0.63 – 1.64)	.940
Adenosquamous	2.41 (1.58 – 3.67)	<.001	2.37 (1.55 – 3.63)	<.001
Grade				
G1	Referent	--	Referent	--
G2	2.64 (1.06 – 6.61)	.038	1.96 (0.76 – 5.08)	.164
G3	4.65 (1.88 – 11.48)	.001	2.86 (1.11 – 7.51)	.030
Unknown	1.60 (0.51 – 5.05)	.420	1.45 (0.45 – 4.70)	.532
Tumor size				
2 cm	Referent	--	Referent	--
> 2 cm	2.56 (1.82 – 3.62)	<.001	1.82 (1.26 – 2.62)	.001
Unknown	NE	.962	NE	.963
Surgery				
Less radical	Referent	--	Referent	--
More radical	1.13 (0.78 – 1.63)	.511	0.99 (0.69 – 1.44)	.969
Positive LN				
No	Referent	--	Referent	--
Yes	3.03 (2.16 – 4.24)	<.001	2.42 (1.70 – 3.42)	<.001
Unknown if examined	NE	.959	NE	.988
*RT				
No	Referent	--	--	--
Yes	3.07 (2.21 – 4.26)	<.001		
*RT type				
None	Referent	--	--	--
External beam	3.10 (2.17 – 4.43)	<.001		
Brachytherapy	5.50 (2.00 – 15.09)	.001		
Both	2.63 (1.55 – 4.49)	<.001		
RT NOS	5.35 (0.74 – 38.59)	.096		

Abbreviations: LN, lymph node; RT, radiation therapy; NOS, not otherwise specified; NE = Not estimable

* Not included in multivariable analysis due to multicollinearity