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The prognostic significance of histology and treatment modality in stage IB1 squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the uterine cervix: SEER study 2004–2008

Znaczenie prognostyczne histologii guza i metody leczenia w przypadku raka płaskonabłonkowego, gruczolakoraka i raka gruczołowo-płaskonabłonkowego szyjki macicy w stadium IB1: badanie zapisów z rejestru SEER dotyczących lat 2004–2008

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Abstract

Objective: To determine the significance of histology and treatment modality on overall survival and cause-specific survival in stage IB1 cervical carcinoma. **Methods:** Cases of stage IB1 squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the uterine cervix managed with either radical hysterectomy, definitive radiation therapy which may include external beam radiation therapy and/or vaginal brachytherapy, or total abdominal hysterectomy with adjuvant radiation therapy which may include external beam radiation therapy plus/minus vaginal brachytherapy were abstracted from the SEER database (2004–2008). Cause-specific survival was calculated using Kaplan–Meier, log-rank, and multivariable Cox regression analyses. **Results:** Five-year cause-specific survival for squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma were 94.4%, 97.3%, and 85.7%, respectively ($p = 0.001$ by log-rank test). On multivariable Cox regression analysis, patients with squamous cell carcinoma were not more likely to die of cervical cancer than patients with adenocarcinoma (hazard ratio = 1.12, 95% confidence interval = 0.53–2.39); but patients with adenosquamous cell carcinoma were more likely to die of cervical cancer than patients with adenocarcinoma (hazard ratio = 3.65, 95% confidence interval = 1.41–9.44). Five-year cause-specific survival was 96.9%, 80.0%, and 92.4% for patients receiving radical hysterectomy, definitive radiation therapy, and total abdominal hysterectomy plus radiation therapy, respectively ($p < 0.0001$ by log-rank test). On multivariable Cox regression analysis, patients who received definitive radiation therapy and patients who received total abdominal hysterectomy plus radiation therapy were more likely to die of cervical cancer than patients who received radical hysterectomy. **Conclusion:** In patients with stage IB1 cervical cancer, on multivariable Cox regression analysis, patients with squamous cell carcinoma were not more likely to die of cervical cancer than patients with adenocarcinoma; patients with adenosquamous cell carcinoma were more likely to die of cervical cancer than patients with adenocarcinoma. Patients who received either definitive radiation therapy or total abdominal hysterectomy plus radiation therapy were more likely to die of cervical cancer than patients who received radical hysterectomy.

Key words: cervical cancer, radiation, surgery

Streszczenie

Cel pracy: Określenie wpływu histologii nowotworu oraz metody leczenia na całkowity czas przeżycia i czas przeżycia swoistego w przypadku raka szyjki macicy w stadium IB1. **Metody:** Analizowano zawarte w rejestrze SEER, obejmujące lata 2004–2008, przypadki raka płaskonabłonkowego, gruczolakoraka i raka gruczołowo-płaskonabłonkowego szyjki macicy w stadium IB1, w których zastosowano radykalną histerektomię, radykalną radioterapię, w tym napromienianie wiązką zewnętrzną i/lub brachyterapię dopochwową, bądź całkowitą histerektomię brzuszną z radioterapią adiuwantową, w tym napromienianie wiązką zewnętrzną z brachyterapią dopochwową lub bez niej. Czas przeżycia swoistego obliczono, wykorzystując analizę Kaplana–Meiera, test log-rank oraz wieloczynnikową analizę regresji Coxa. **Wyniki:** Pięcioletnie przeżycie swoiste w przypadku raka płaskonabłonkowego, gruczolakoraka oraz raka gruczołowo-płaskonabłonkowego wynosiło odpowiednio 94,4%, 97,3% i 85,7% ($p = 0{,}001$ wg testu log-rank). Wieloczynnikowa analiza regresji Coxa wykazała,

że prawdopodobieństwo zgonu z powodu raka szyjki macicy u pacjentek z rakiem płaskonabłonkowym nie było wyższe niż u pacjentek z gruczolakorakiem (współczynnik ryzyka = 1,12; przedział ufności 95% = 0,53–2,39). Z kolei u pacjentek z rakiem gruczołowo-płaskonabłonkowym prawdopodobieństwo zgonu z powodu tego nowotworu było wyższe niż u pacjentek z gruczolakorakiem (współczynnik ryzyka = 3,65, przedział ufności 95% = 1,41–9,44). Pięcioletnie przeżycie swoiste wynosiło 96,9%, 80,0% i 92,4% u chorych, które zostały poddane odpowiednio radykalnej histerektomii, radykalnej radioterapii oraz całkowitej histerektomii brzusznej z radioterapią ($p < 0,0001$ wg testu log-rank). Wieloczynnikowa analiza regresji Coxa wykazała większe prawdopodobieństwo zgonu z powodu raka szyjki macicy u pacjentek, które zostały poddane radykalnej radioterapii, oraz tych, które przeszły zabieg całkowitej histerektomii brzusznej z radioterapią, w porównaniu z chorymi, które poddano radykalnej histerektomii. **Wniosek:** U chorych na raka szyjki macicy w stadium IB1 wieloczynnikowa analiza regresji Coxa wykazała, że prawdopodobieństwo zgonu z powodu raka szyjki macicy u pacjentek z rakiem płaskonabłonkowym nie było większe niż u pacjentek z gruczolakorakiem, z kolei u chorych z rakiem gruczołowo-płaskonabłonkowym było wyższe niż u pacjentek z gruczolakorakiem. U pacjentek, które zostały poddane radykalnej radioterapii lub przeszły zabieg całkowitej histerektomii brzusznej z radioterapią, prawdopodobieństwo zgonu z powodu raka szyjki macicy było większe niż u chorych, które poddano radykalnej histerektomii.

Słowa kluczowe: rak szyjki macicy, radioterapia, operacja

INTRODUCTION

Cervical cancer is the second most common cancer among women between the ages of 15–44 worldwide, with an estimated 527,624 new cases and 265,653 deaths annually[1]. In the past, cervical cancer was one of the leading causes of cancer death for US women. Over the past 40 years, the number of deaths decreased dramatically largely due to the nationwide implementation of effective cervical cancer screening methods[2]. Still, in the US an estimated 12,360 new cases and 4,020 deaths from cervical cancer were expected to occur in 2014[3].

Approximately 50% of the cervical cancers in the US are diagnosed while the cancer is organ-confined[4]. Stage IA patients have an excellent 5-year survival rate of 95–100%, while stage IB patients have a more variable 5-year survival ranging from 60 to 90%[4,5]. Both primary surgical resection and definitive radiation therapy are acceptable treatment options for stage I cervical cancer[6]. The majority (75–80%) of the cervical cancers are squamous cell carcinomas (SCC), with the remainder (20–25%) comprised of the adenocarcinoma (AC) and adenosquamous (ASC) types; rare tumor types such as lymphoma, sarcoma, and melanoma account for less than 1% of all cervical cancers[7,8].

FIGO stage IB1 cervical cancer is defined as either 1) microscopic disease that is more than 5 millimeters deep and more than 7 millimeters wide or 2) macroscopic disease that is up to 4 cm in diameter. The National Comprehensive Cancer Network (NCCN) guidelines recommend one of two treatment approaches for stage IB1 disease: 1) radical hysterectomy (RAH) + pelvic lymph node dissection ± para-aortic lymph node sampling or 2) pelvic external beam radiotherapy (EBRT) + vaginal brachytherapy (VBT) ± concurrent cisplatin-based chemotherapy. Recently, many patients have been treated with total abdominal hysterectomy (TAH) followed by adjuvant EBRT ± brachytherapy.

The aim of the current study is to examine the prognostic significance of histology and treatment modality in patients in the SEER database recently diagnosed with and treated for stage IB1 carcinoma of the uterine cervix.

METHODS

The SEER database collects cancer data from seventeen population-based cancer registries, and covers approximately 28% of US population[4]. We used the SEER (2004–2008) database to abstract patient demographics, tumor characteristics, and treatment modality for histologically confirmed FIGO stage IB1 carcinoma of the uterine cervix. The data was collected from 17 registries (including Alaska, Atlanta, California excluding SF/SJM/LA, Connecticut, Detroit, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Rural Georgia, San Francisco, San Jose-Monterey, Seattle, Utah), and a total of 3,735 cases were identified. From these data we included patients diagnosed with SCC (ICD-03 codes 8052, 8070, 8071, 8072, 8076, 8082, 8083), AC (ICD-03 codes 8140, 8210, 8200, 8255, 8260, 8261, 8262, 8310, 8323, 8380, 8384, 8441, 8460, 8480, 8482, 8490), and ASC (ICD-03 codes 8015, 8481, 8560), and patients treated with RAH alone, definitive EBRT plus VBT, or TAH with adjuvant radiation (EBRT ± VBT). We excluded patients who were treated with RAH with VBT alone without EBRT as this was not recommended in the most recent updates of the national guidelines[9].

Statistical analysis

Descriptive statistics (including mean, standard deviation, median, range, frequency, and percent) were calculated to characterize the study cohort in relation to demographic, prognostic, and treatment factors of interest. The primary endpoints were overall survival (OS) and cause-specific survival (CSS). CSS was ascertained by selecting cervix cancer as the cause of death in the SEER database search. Deaths due to causes other than cervix cancer were censored when estimating CSS. CSS was defined as the time

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from diagnosis until death from cervix cancer (or until date of last follow-up or death from other cause). OS was defined as the time from diagnosis until death from any cause (or until date of last follow-up if alive). Kaplan–Meier survival analysis was performed to evaluate OS/CSS and the log-rank test was employed to compare OS/CSS between 1) the three treatment modalities of interest (i.e., definitive radiation therapy – RT, RAH only, and TAH + RT), 2) the three histological subtypes of interest (i.e., SCC, AC, and ASC), and 3) other demographic/prognostic factors of interest (i.e., age, race, grade). Multivariable Cox proportional hazards regression analysis was performed to estimate the independent effect of treatment modality on CSS, controlling for histology, grade, and race. Competing-risks survival regression was also performed to adjust the multivariable CSS hazard ratios (HR) for the competing event of death due to causes other than cervix cancer (based on Fine and Gray's proportional subhazards model). Kaplan–Meier analysis (comparing OS/CSS between the three treatment modalities) was also stratified by histology category. All *p* values are two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (95% CI) for HRs and subhazard ratios were calculated to assess the precision of the obtained estimates. All analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL) and Stata Version 13.0 (StataCorp, College Station, TX).

RESULTS

The analysis included a total of 1,217 patients with histologically confirmed FIGO stage IB1 SCC, AC, and ASC of the uterine cervix, diagnosed and treated between 2004 and 2008. Tab. 1 lists the patient demographics and tumor characteristics. Out of the study population, 9.3% were African-American, 79.8% were Caucasian, and 10.8% were classified as Other. In our study population, 53.8% had SCC histology, 32.0% had AC, and 6.3% had ASC; 7.3% had histology listed as other or unavailable; 15.4% had grade 1 disease, 39.8% had grade 2, 32.0% had grade 3, and 2.1% had grade 4.

Race	
African-American	9.3%
Caucasian	79.8%
Other	10.8%
Histology	
Squamous-cell carcinoma	53.8%
Adenocarcinoma	32.0%
Adenosquamous cell carcinoma	6.3%
Grade	
1	15.4%
2	39.8%
3	32.0%
4	2.1%

Tab. 1. Study population characteristics (n = *1,217)*

The OS rates at 60 months for SCC, AC, and ASC were 90.7%, 94.8%, and 79.0%, respectively (Fig. 1). The difference between the three groups was statistically significant ($p = 0.001$ by log-rank test). The CSS rates at 60 months for SCC, AC, and ASC were 94.4%, 97.3%, and 85.7%, respectively (Fig. 2). The difference between the three groups was statistically significant ($p = 0.001$ by log-rank test). On multivariable Cox regression analysis (Tab. 2), patients with SCC were not more likely to die of cervical cancer than patients with AC (HR = 1.12, 95% CI = 0.53–2.39).

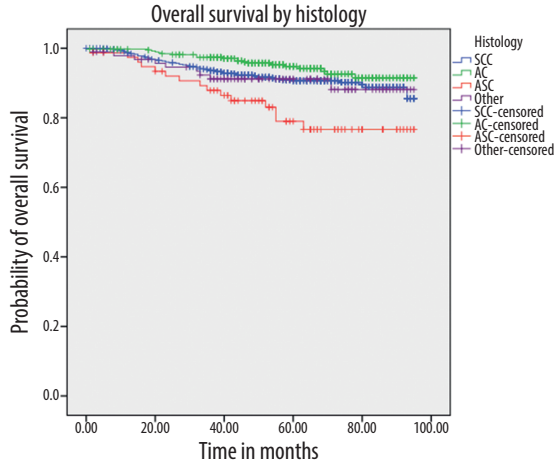

Fig. 1. Kaplan–Meier curve for OS by histology; SCC 60-month OS was 90.7%, AC 60-month OS was 79.0%, and ASC 60-month OS was 79.0%; p = *0.001 by log-rank test*

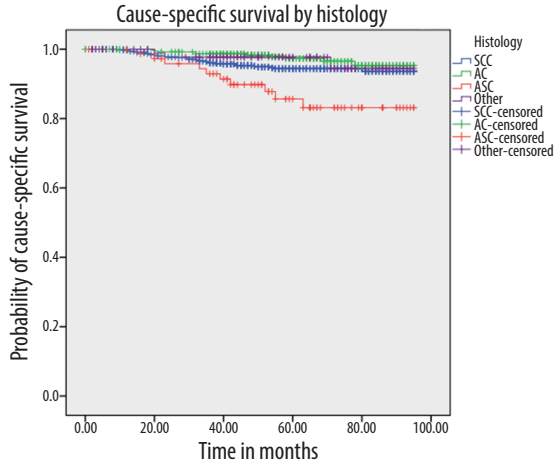

Fig. 2. Kaplan–Meier curve for CSS by histology; SCC 60-month CSS was 94.4%, AC 60-month CSS was 97.3%, and ASC 60-month CSS was 85.7%; p = *0.001 by log-rank test*

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Predictor	*p* value	Adjusted HR	95.0% CI for HR	
			Lower	Upper
Modality = RAH	(referent)			
Modality = Def. RT	<0.0001	8.28	4.02	17.02
Modality = TAH + RT	0.001	2.96	1.53	5.70
Grade = III/IV	0.02	2.08	1.13	3.83
Histology = AC	(referent)			
Histology = SCC	0.77	1.12	0.53	2.39
Histology = ASC	0.008	3.65	1.41	9.44
Histology = Other	0.35	0.37	0.05	2.95
Race = White	(referent)			
Race = Black	0.30	1.50	0.69	3.26
Race = Other	0.21	1.69	0.75	3.82

Tab. 2. Multivariable Cox regression model for predictors of CSS

Patients with ASC were more likely to die of cervical cancer than patients with AC (HR = 3.65, 95% CI = 1.41–9.44). The survival rates according to treatment modality were also analyzed. The 60-month OS rates for patients with stage IB1 were 94.0%, 75.4%, and 85.6% for RAH, definitive RT, and TAH + RT, respectively (Fig. 3). There was a statistically significant difference in OS between the three treatment types ($p < 0.0001$ by log-rank test). The 60-month CSS rates were 96.9%, 80.0%, and 92.4% for RAH, definitive RT, and TAH + RT, respectively (Fig. 4). There was a statistically significant difference in CSS between the three treatment types ($p < 0.0001$ by log-rank test).

On multivariable Cox regression analysis (Tab. 2), patients who were treated with definitive RT were more likely to die of cervical cancer than patients who received RAH (HR = 8.28, 95% CI = 4.02–17.02). Patients who received TAH + RT were more likely to die of cervical cancer than patients who received RAH (HR = 2.96, 95% CI = 1.53–5.70).

An attempt was made to analyze the effect of treatment modality on OS and CSS for each histologic type alone. The 60-month OS rates for patients with stage IB1 SCC were 94.1%, 76.6%, and 84.0% for RAH, definitive RT, and TAH + RT, respectively (Fig. 5). There was a statistically

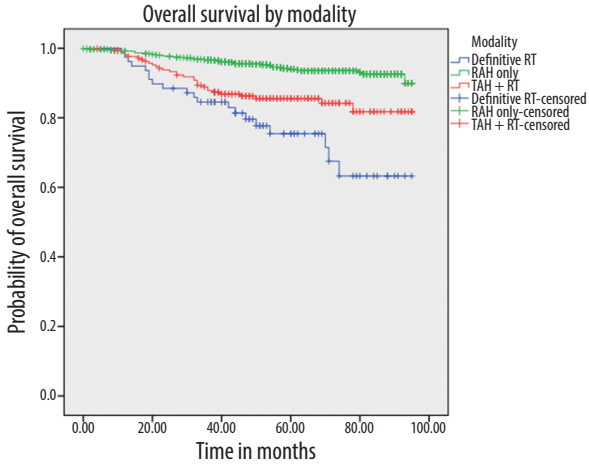

Fig. 3. Kaplan–Meier curve for OS by treatment modality; definitive RT 60-month OS was 75.4%, RAH 60-month OS was 94.0%, and TAH + RT 60-month OS was 85.6%; p < 0.0001 by log-rank test

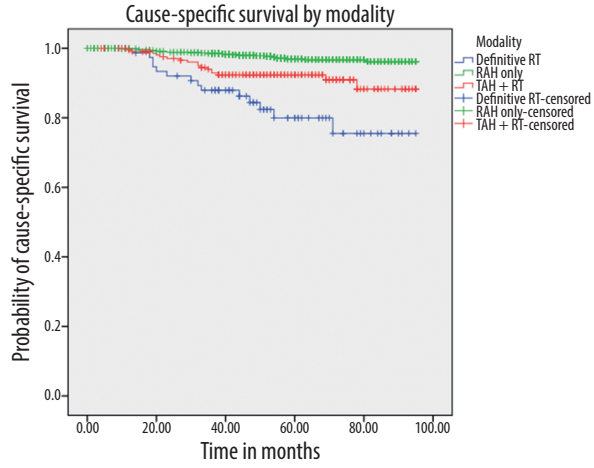

Fig. 4. Kaplan–Meier curve for CSS by treatment modality; definitive RT 60-month CSS was 80.0%, RAH 60-month CSS was 96.9%, and TAH + RT 60-month CSS was 92.4%; p < 0.0001 by log-rank test

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significant difference in OS between the three treatment types ($p < 0.0001$ by log-rank test). The 60-month CSS rates for SCC patients were 97.3%, 81.3%, and 89.1% for RAH, definitive RT, and TAH + RT, respectively (Fig. 6). There was a statistically significant difference in CSS between the three treatment types ($p < 0.0001$ by log-rank test). The 60-month OS rates for patients with stage IB1 AC were 97.0%, 64.9%, and 89.5% for RAH, definitive RT, and TAH + RT, respectively (see supplemental Fig. 7). There was a statistically significant difference in OS between the three treatment types ($p < 0.0001$ by log-rank test). Unfortunately, there were an inadequate number of events to calculate CSS for AC or ASC by treatment modality, and also an inadequate number of events to calculate OS for ASC by treatment modality.

There was a non-significant trend towards higher age at diagnosis for African-American patients than for White or Other patients ($p = 0.13$ by chi-square test). The effects of grade on CSS were also analyzed. On univariate analysis, grade 3 or 4 disease had worse CSS as compared to grade 1 or 2 disease ($p < 0.0001$). Multivariable Cox regression demonstrated an increased risk of death from the disease with grade 3 or 4 disease as compared to grade 1 or 2 disease (HR = 2.08, 95% CI = 1.13–3.83). Adjustment for other causes of death (i.e., using competing-risks regression) did not materially alter the multivariable HRs or p values noted above.

DISCUSSION

The incidence of SCC is decreasing while the incidence of AC and ASC is increasing[8,10,11].

This makes understanding the impact of histology on clinical outcomes especially important.

In our study of patients with stage IB1 cervical carcinoma, histology was found to have a significant influence on CSS after adjusting for confounding factors. On multivariable analysis, ASC histology was found to have a significantly decreased CSS when compared with AC (HR = 3.65, 95% CI = 1.41–9.44). SCC was not found to have a significant difference in CSS when compared with AC on multivariable analysis.

A review of the literature identified other analyses of the impact of histology on CSS in cervical cancer, as summarized in Tab. 3.

Galic *et al.* analyzed 24,562 patients from the SEER database with stage IB1–IIA disease. They found that patients with AC had an increased HR of death from cervical cancer than patients with SCC (HR = 1.39, 95% CI = 1.23–1.56). They also found that patients with ASC had an increased HR of death from cervical cancer than patients with SCC (HR = 1.55, 95% CI = 1.32–1.82)[12].

Look *et al.* published data from a prospective trial examining 813 cervical cancer patients with stage IB disease treated surgically. They found that patients with ASC had an increased HR of death from cervical cancer than patients

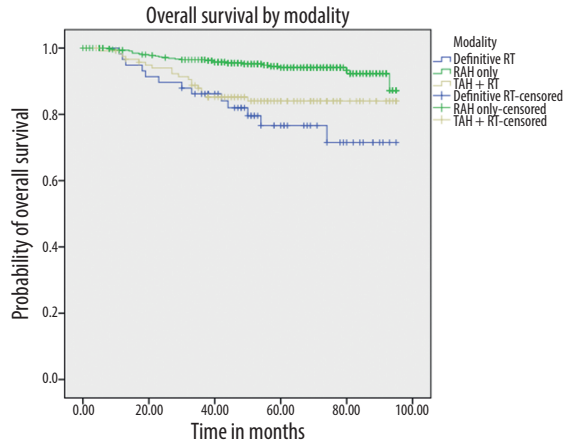

Fig. 5. Kaplan–Meier curve for OS by treatment modality for SCC only; definitive RT 60-month OS was 76.6%, RAH 60-month OS was 94.1%, and TAH + RT 60-month OS was 84.0%; p < *0.0001 by log-rank test*

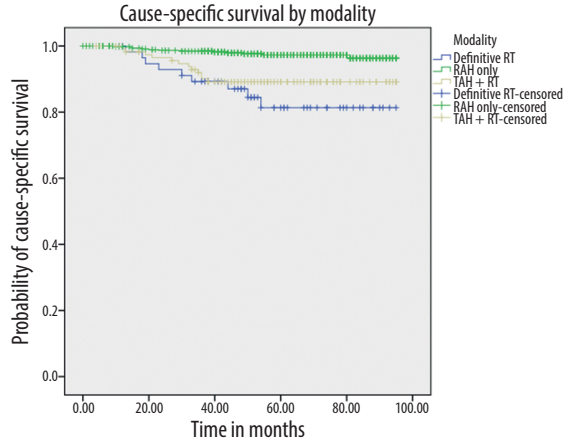

Fig. 6. Kaplan–Meier curve for CSS by treatment modality for SCC only; definitive RT 60-month CSS was 81.3%, RAH 60-month CSS was 97.3%, and TAH + RT 60-month CSS was 89.1%; p < *0.0001 by log-rank test*

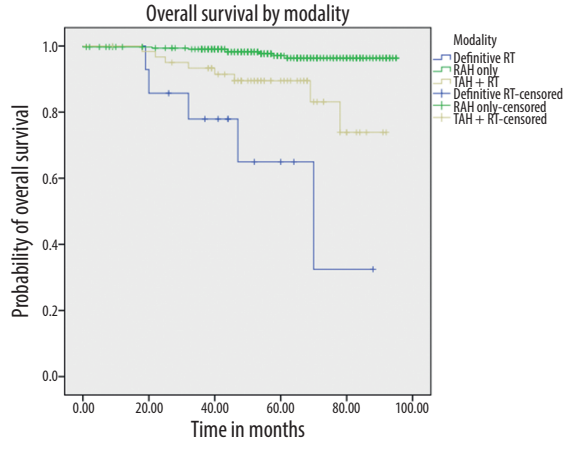

Fig. 7. Kaplan–Meier curve for OS by treatment modality for AC only; definitive RT 60-month OS was 64.9%, RAH 60-month OS was 97.0%, and TAH + RT 60-month OS was 89.5%; p < *0.0001 by log-rank test*

Histology	Stage(s)	HR of death	95% CI	*p* value	Referent histology	Source	Number of patients	Source of patients	Category
ASC	IB1	3.65	1.41–9.44	SS	AC	Current series	1217	SEER	Retrospective
SCC	IB1	1.12	0.53–2.39	NS	AC	Current series	1217	SEER	Retrospective
AC	IB1–IIA	1.39	1.23–1.56	SS	SCC	Galic *et al.*	24562	SEER	Retrospective
ASC	IB1–IIA	1.55	1.32–1.82	SS	SCC	Galic *et al.*	24562	SEER	Retrospective
ASC	IB	2.8	1.3–6.1	SS	AC	Look *et al.*	813	GOG Study	Prospective
ASC	IB	1.8	1.1–3.0	SS	SCC	Look *et al.*	813	GOG Study	Prospective
ASC	I–IV	1.35	1.20–1.51	SS	SCC	Vinh-Hung *et al.*	30989	SEER	Retrospective
Non-mucinous AC	I–IV	1.06	0.98–1.15	NS	SCC	Vinh-Hung *et al.*	30989	SEER	Retrospective
Mucinous AC	I–IV	1.52	1.12–1.88	SS	SCC	Vinh-Hung *et al.*	30989	SEER	Retrospective

Tab. 3. Published series on impact of histology on CSS in cervical cancer

with AC (HR = 2.8, 95% CI = 1.3–6.1). Patients with ASC also had an increased HR of death from cervical cancer than patients with SCC (HR = 1.8, 95% CI = 1.1–3.0)[13].

Vinh-Hung *et al.* analyzed 30,989 patients from the SEER database with stage I–IV disease. Patients with ASC had an increased HR of death from cervical cancer as compared to patients with SCC (HR = 1.35, 95% CI = 1.20–1.51). Patients with non-mucinous AC were not at an increased risk of death from cervical cancer (HR = 1.06, 95% CI = 0.98–1.15). Patients with mucinous AC were at an increased risk of death from cervical cancer (HR = 1.52, 95% CI = 1.12–1.88)[11].

As a group, these analyses seem to suggest ASC and AC have worse CSS than SCC, and that ASC has a worse CSS than AC, although a rigorous meta-analysis is outside of the scope of this discussion. Our data did not find a significant difference in CSS between AC and SCC; this may be due to our relatively small sample size compared to the other two SEER analyses described, or due to other limitations inherent to SEER which are described further below.

In early stage cervical carcinoma, both surgery and RT have been acceptable primary modalities of treatment[14]. In a landmark prospective trial, Landoni *et al.* examined 469 women with newly diagnosed stage IB and IIA cervical carcinoma and randomized them to RAH or radiotherapy (pelvic EBRT + VBT). Postoperative RT was given to patients with at least one pathologic risk factor identified during surgery. This study found no significant difference in OS or disease-free survival (DFS) between the two arms[6].

In our study, comparing the outcomes of IB1 cervical carcinoma patients according to treatment type, definitive RT was associated with poorer outcomes. On multivariable Cox regression analysis, patients who were treated with definitive RT were more likely to die of the disease than patients who received RAH (HR = 8.28, 95% CI = 4.02–17.02). Patients who received TAH + RT were more likely to die of the disease than patients who received RAH (HR = 2.96, 95% CI = 1.53–5.70). These findings do not concur with the results of the Landoni trial.

One possible explanation is the different distribution of histologies between the two study populations. In the Landoni trial, 88% of the study population was comprised of SCC, with the remainder being AC (10%) and small cell carcinoma (2%). In our study, 53.8% of our IB1 study population had SCC, 32.0% had AC, and 6.8% had ASC, with 7.8% of patients having other or unspecified histology. The result could reflect a decreased response of AC and ASC to radiation, as 38.8% of our IB1 population had AC or ASC. Indeed, 60-month OS was worse for AC patients treated with definitive RT than for SCC patients treated with definitive RT (64.9% versus 76.6%). However, given that these findings emerge from a subgroup analysis, caution should be taken in interpreting the results.

Currently, data on the clinical efficacy of RT for AC and ASC are limited. Eifel *et al.* retrospectively examined 160 patients with stage I AC of the cervix treated with either RAH, definitive RT, or TAH followed by adjuvant RT. The 5-year survival rates were similar in all three groups, but in a subgroup analysis pelvic recurrence was higher in the RAH group when the tumor size was 3 to 4 cm[9]. These investigators suggested that RT was effective against AC, and may be the preferred mode of treatment in larger AC tumors. Huang *et al.* retrospectively reviewed 148 patients with stage I–IVA AC or ASC of the cervix treated with definitive RT. The 5-year DFS for AC or ASC was 68% for non-bulky stage IB–IIA (tumor size ≤4 cm) and 38% for bulky stage IB–IIA (tumor size >4 cm), which was 20–35% lower than the updated 5-year DFS for their SCC population from a previous study. Furthermore, a greater proportion of AC or ASC tumors had residual disease after pelvic RT versus SCC[15]. These findings suggested a decreased response of AC or ASC tumors to RT.

However, there are a few inherent weaknesses to SEER that should cause any analysis of this database to be interpreted with caution. There is no central pathologic review or review of staging. There is also no quality assurance or review of how radiation was delivered. There is no chart review to determine if data was entered accurately into the database. There are several additional weaknesses inherent to a SEER-based analysis of outcomes in cervical cancer. Our results could be due to selection bias if we hypothesize that a greater proportion of patients were given definitive radiation due to their ineligibility for surgery. Also, information on preoperative imaging is not available in the SEER database. Patients with findings suspicious for more advanced disease on such imaging may have been treated with radiotherapy rather than surgery, although this reasoning would not be documented in the SEER database. In addition, certain pathologic characteristics not documented in the SEER database, such as lymphovascular space invasion, are negative prognostic factors for this disease; clinicians may have referred these patients with a worse prognosis for radiation instead of surgery. Another inherent limitation of a SEER analysis is that clinically staged patients may have been upstaged based on intra-operative findings obtained through TAH or RAH. These higher-stage patients may have therefore been excluded from the analysis. All of these weaknesses could generate biases which would favor a better CSS in the surgical groups than in the definitive RT group.

In view of this, it must be underscored that the findings of this retrospective study are not meant to direct or change the current management of stage IB1 cervical cancer. Rather, they indicate the need for further prospective studies to determine the optimal treatment strategy. In particular, it remains possible that different histologies of cervical cancer may require different therapeutic approaches, such as modifying the radiation dose to achieve maximum response. Especially in light of the changing patterns of histology in cervical cancer, this is a hypothesis which is important to investigate further.

Conflict of interest

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References

1. ICO Information Centre on HPV and Cancer (HPV Information Centre): Human Papillomavirus and Related Diseases Report. Available from: www.hpvcentre.net/statistics/reports/XWX.pdf, 2016.
2. National Institutes of Health: Cervical Cancer. NIH Consensus Statement 1996; 14: 1–38.
3. National Cancer Institute: Cervical Cancer. Available from: http://www.cancer.gov/cancertopics/types/cervical, 2015.
4. Howlader N, Noone AM, Krapcho M *et al.*: SEER Cancer Statistics Review, 1975–2008. National Cancer Institute, Bethesda, MD. Available from: http://seer.cancer.gov/csr/1975_2008/. 2011.
5. Greene FL, Page DL, Fleming ID *et al.*: AJCC Cancer Staging Manual. 6th ed., Springer, New York 2002.
6. Landoni F, Maneo A, Colombo A *et al.*: Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. Lancet 1997; 350: 535–540.
7. Pazdur R, Wagman LD, Comphausen KA *et al.* (eds.): Cancer Management: A Multidisciplinary Approach. 13th ed., UBM Medica, Norwalk 2010.
8. Smith HO, Tiffany MF, Qualls CR *et al.*: The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States – a 24-year population-based study. Gynecol Oncol 2000; 78: 97–105.
9. Eifel PJ, Burke TW, Delclos L *et al.*: Early stage I adenocarcinoma of the uterine cervix: treatment results in patients with tumors less than or equal to 4 cm in diameter. Gynecol Oncol 1991; 41: 199–205.
10. Liu S, Semenciw R, Mao Y: Cervical cancer: the increasing incidence of adenocarcinoma and adenosquamous carcinoma in younger women. CMAJ 2001; 164: 1151–1152.
11. Vinh-Hung V, Bourgain C, Vlastos G *et al.*: Prognostic value of histopathology and trends in cervical cancer: a SEER population study. BMC Cancer 2007; 7: 164.
12. Galic V, Herzog TJ, Lewin SN *et al.*: Prognostic significance of adenocarcinoma histology in women with cervical cancer. Gynecol Oncol 2012; 125: 287–291.
13. Look KY, Brunetto VL, Clarke-Pearson DL *et al.*: An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1996; 63: 304–311.
14. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. In: National Comprehensive Cancer Network. Available from: www.nccn.org/professionals/physician_gls/pdf/cervical.pdf, 2012.
15. Huang YT, Wang CC, Tsai CS *et al.*: Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. Int J Radiat Oncol Biol Phys 2011; 80: 429–436.