Am J Cancer Res 2021;11(4):1719-1732
www.ajcr.us /ISSN:2156-6976/ajcr0128247

Original Article

Contemporary external beam radiotherapy boost or high dose-rate brachytherapy boost for cervical cancer: a propensity-score-matched, nationwide, population-based cohort study

Jiaqiang Zhang[1*], Mingyang Sun[1*], Ningtao Li[1], Mengrong Miao[1], Yitian Yang[1], Han-Chuan Hsu[2*], Ho-Min Chen[3,4], Szu-Yuan Wu[3,4,5,6,7,8,9]

[1]Department of Anesthesiology and Perioperative Medicine, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Zhengzhou, Henan, China; [2]Department of Obstetrics and Gynecology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [3]Department of Food Nutrition and Health Biotechnology, College of Medical and Health Science, Asia University, Taichung, Taiwan; [4]Big Data Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [5]Division of Radiation Oncology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [6]Department of Healthcare Administration, College of Medical and Health Science, Asia University, Taichung, Taiwan; [7]Cancer Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [8]Graduate Institute of Business Administration, Fu Jen Catholic University, Taipei, Taiwan; [9]Centers for Regional Anesthesia and Pain Medicine, Taipei Municipal Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan. [*]Equal contributors.

Received December 14, 2020; Accepted February 17, 2021; Epub April 15, 2021; Published April 30, 2021

Abstract: To estimate the survival effects of contemporary external beam radiotherapy (EBRT) boost modalities (intensity-modulated radiation therapy or volumetric modulated arc therapy) and high dose-rate brachytherapy (HDR-BT) boost in patients with cervical cancer (CC). Patients who had been diagnosed as having CC were recruited from the Taiwan Cancer Registry Database. Propensity score matching was performed, and Cox proportional-hazards model curves were used to analyze the all-cause mortality of patients who received standard whole-pelvis irradiation with different boost modalities. The matching process yielded a final cohort of 1,630 patients (815 in the EBRT boost and HDR-BT boost groups, respectively) eligible for further analysis. The multivariate Cox regression analyses indicated that the adjusted hazard ratio (95% confidence intervals) for EBRT boost compared with HDR-BT boost was 1.62 (1.43-1.84). Multivariable analysis revealed that the independent poor prognostic factors of all-cause mortality among patients with CC were adenocarcinoma, no chemotherapy, Charlson comorbidity index score ≥ 1, age ≥ 60 years, and advanced International Federation of Gynecology and Obstetrics stage. HDR-BT boost may be more beneficial than contemporary EBRT boost in selected patients with CC.

Keywords: Cervical cancer, external beam radiotherapy, brachytherapy, boost, high dose rate

Introduction

Cervical cancer (CC) is the third most common gynecologic cancer diagnosis and cause of gynecologic cancer death in the United States and is ranked as the cancer with the ninth highest number of deaths in Taiwan [5, 6]. CC currently has a lower incidence and a lower mortality rate than uterine corpus and ovarian cancer as well as numerous other cancers, both in the United States and Taiwan [5-7]. However, CC remains a considerable cause of cancer morbidity and mortality in countries that do not have access to CC screening and prevention programs [8, 9]. Women with locally advanced CC have higher rates of recurrence and lower survival rates than those with early disease stages [10].

For most women, radiotherapy (RT; in conjunction with chemotherapy) is applied to the pelvis using external beam RT (EBRT) [11, 12]. Cervical brachytherapy (BT)-boost is also administered to maximize local control [13]. BT boost is the local application of radiation to the cervix and part of the vagina [13]. BT boost is an essential component of treatment for locally advanced CC and allows for a higher dose of RT

to be administered to the cervix while sparing the surrounding normal tissue [13-15]. BT boost is initiated when optimal tumor reduction is achieved after EBRT [13]. Adequate cervical regression typically occurs after 2-5 weeks of therapy, depending on the presenting tumor stage and size and response to therapy [16-22]. BT boost can be delivered with either a low-dose-rate (LDR) or high-dose-rate (HDR) system [16-22]. The International Commission on Radiation Units defines LDR-BT as 0.4 to 2 Gy/hour, whereas HDR-BT is delivered at > 12 Gy/hour [16-22]. LDR-BT requires one or two insertions and can be initiated near or after the completion of EBRT. The number of HDR insertions varies by institution but is most commonly in the range of three to six [16-22]. The dose delivered per HDR-BT procedure is adjusted to account for the total number of insertions [23]. Dosimetry and isodose curve distributions may differ for different insertions [23]. The techniques applied for HDR-BT insertions also differ between high-volume and low-volume hospitals [13-15, 24].

Quality research in radiation oncology revealed that the percentage of patients not receiving BT boost increased from 6% in a 1996 to 1999 survey to 13% in a 2005 to 2007 survey [15]. Furthermore, only 65% of patients who received BT boost were treated in a facility that treated fewer than three patients with intact CC per year [13-15]. Therefore, interest has increased in the use of alternatives to BT boost for delivering this consolidative dose of EBRT boost to the cervix because the use of BT boost is limited in nonacademic and low-volume hospitals [5, 24-27]. Contemporary EBRT techniques, such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), have been assessed because of their ability to deliver a highly conformal dose [2]. Dosimetric analyses and limited single-institution experiences have demonstrated the feasibility of the contemporary EBRT boost approach [3, 4]. These findings have led to concern regarding increasing the use of contemporary EBRT boost modalities (IMRT or VMAT) and reducing the use of HDR-BT with limited comparative outcome-based data, especially in Asia. Therefore, we aimed to estimate the survival effects of contemporary EBRT boost modalities (IMRT or VMAT) and HDR-BT boost in patients with CC. We thus performed propensity score matching (PSM) between cohorts to obtain comparative data.

Patients and methods

Data source

A CC cohort was established using data from the Taiwan Cancer Registry Database (TCRD), maintained by the Collaboration Center of Health Information Application. Patients diagnosed as having CC between January 1, 2008, and December 31, 2016, who received standard whole-pelvis radiotherapy (WPRT) followed by EBRT boost or HDR-BT boost were included. The follow-up duration was from the index date to December 31, 2017. The TCRD contains detailed cancer-related information on patients, including the International Federation of Gynecology and Obstetrics (FIGO) clinical stage, treatment modalities, pathologic data (including pathologic stage), hospital level, irradiation doses, chemotherapy doses, and chemotherapy regimens [28-35].

Study cohort

The protocols were approved by the Institutional Review Board of Taipei Medical University. Patient diagnoses were confirmed using their pathological data, and patients who received a new diagnosis of CC were confirmed to have no other cancer or distant metastasis. The standard WPRT consisted of a 45-Gy external beam delivered to the pelvis in 25 fractions of 1.8 Gy and a parametrium boost of 50-54 Gy or bulky lymph node boost of 60 Gy using IMRT or VMAT techniques. EBRT boost using IMRT or VMAT techniques was applied to the gross cervical tumor. The median total dose of EBRT boost was 25.2 Gy, with a median fraction size of 1.8 Gy. Moreover, the International Committee on Radiation Units and Measurements' Report 38 outlines the most commonly applied conventions for prescribing BT boost dose points [36]. The radiation dose should be administered to point A, a point located 2 cm superior and 2 cm lateral to the cervical os, along the plane perpendicular to the intrauterine tandem [37]. In Taiwan, HDR-BT is generally performed using high-dose Ir-192 and LDR-BT is not applied for CC treatment [5]. BT boost involves the application of HDR-BT to point A with a median total dose of 25 Gy in five fractions. The timeline of EBRT boost or IC HDR-BT boost was shown as

Supplementary Figure 2. Patients were enrolled in this study if they received a chemotherapy regimen that was a platinum-based regimen applied with concurrent RT. For women with locally advanced CC (stage IB3-IVA), primary concurrent chemoradiotherapy would be administrated according to the National Comprehensive Cancer Network guidelines [38]. Other inclusion criteria were age ≥ 20 years and AJCC stage I-IVA. Patients with metastasis, an age of < 20 years, nonstandard WPRT, unclear chemotherapy regimen and dosage, unclear pathologic type, missing information on irradiation boost modality or RT dose, and unclear staging were excluded. Furthermore, patients with non-platinum-based regimens, immunotherapy, non-IMRT, non-VMAT techniques, stereotactic body radiation therapy (SBRT) boost, and nonrecorded hospital type (academic center or community hospital) were excluded from our cohorts [39].

Finally, patients with CC who received standard WPRT followed by contemporary EBRT boost (IMRT or VMAT) or HDR-BT boost were enrolled and grouped according to whether they received EBRT boost or BT boost. The index date was the date of CC diagnosis. Comorbidities were assessed using the Charlson comorbidity index (CCI) [40, 41]. Only comorbidities noted within 6 months of the index date were included. Comorbidities were identified using the main International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes; diseases recorded at the first admission or identified more than twice during outpatient visits were included as comorbidities.

Covariates

After adjustment for confounders, a Cox proportional-hazards model was established to model the time from the index date until all-cause mortality in patients with CC. PSM was performed to reduce the effects of potential confounding factors during comparisons of therapy outcomes between boost groups. The logits of the propensity scores were matched using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score [42]. Matching is a common technique adopted for selecting controls with the same background covariates as case participants, thus minimizing any difference between the two individuals that the investigator believes must be controlled for. All covariates in the HDR-BT boost group, such as age, year of diagnosis, pathologic type, FIGO stage, platinum cumulative dose, CCI score, income, hospital level, and hospital area, were matched through PSM at a 1:1 ratio with those in the EBRT boost group [43].

Statistical analysis

A Cox model was used to regress survival on treatment status using a robust sandwich estimator to account for clustering within matched sets [44]. Multivariate Cox regression analysis was performed to calculate hazard ratios (HRs) to determine whether age, year of diagnosis, pathologic type, FIGO stage, RT boost dose, platinum cumulative dose, CCI score, income, hospital level, and hospital area were independent predictors of treatment choice. Potential predictors were controlled for in the analysis (**Table 1**). The endpoint was all-cause mortality in the two RT boost treatment groups, with the HDR-BT boost group serving as the reference group. Cox proportional-hazards regression analysis was performed on the risk of all-cause mortality, stratified by FIGO stage. Adjusted HRs (AHRs) of all-cause mortality for the PSM cohorts, stratified by boost modality (IMRT or VMAT) and dosage (< 20 Gy boost or ≥ 20 Gy boost), were estimated and compared with those for HDR-BT boost. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). $P < 0.05$ in a two-tailed Wald test was considered significant.

The cumulative incidence of overall survival (OS) was estimated using the Kaplan-Meier method, and differences between RT boost modalities were determined using a stratified log-rank test to compare survival curves (stratify on matched sets) [45]. $P < 0.05$ in a two-tailed Wald test was considered significant.

Results

Clinicopathological characteristics

The matching process yielded a final cohort of 1,630 patients (815 and 815 in EBRT boost group and HDR-BT-boost group, respectively) who were eligible for further analysis; participant characteristics are summarized in **Table 1**. The age distribution was balanced with

Table 1. Characteristics of patients with cervical cancer in propensity score-matched cohorts receiving different contemporary local boost modalities

Variable		Total (N = 1,630)		EBRT boost (N = 815)		IC HDR-BT boost (N = 815)		*P* value
		n	(%)	n	(%)	n	(%)	
Age, years	20-49	314	(19.3)	157	(19.3)	157	(19.3)	1.0000
	50-59	370	(22.7)	185	(22.7)	185	(22.7)	
	60-69	272	(16.7)	136	(16.7)	136	(16.7)	
	≥ 70	674	(41.3)	337	(41.3)	337	(41.3)	
Year of diagnosis	2008-2010	423	(26.0)	210	(25.8)	213	(26.1)	0.8763
	2011-2013	686	(42.1)	340	(41.7)	346	(42.5)	
	2014-2016	521	(32.0)	265	(32.5)	256	(31.4)	
Pathologic types	SCC	1403	(86.1)	700	(85.9)	703	(86.3)	0.8264
	Other	227	(13.9)	115	(14.1)	112	(13.7)	
FIGO stage	IA1	51	(3.1)	25	(3.1)	25	(3.1)	1.0000
	IA2	102	(6.3)	51	(6.3)	51	(6.3)	
	IB	155	(9.5)	78	(9.5)	78	(9.3)	
	IIA	186	(11.4)	93	(11.4)	93	(11.4)	
	IIB	476	(29.2)	238	(29.2)	238	(29.2)	
	IIIA	268	(16.4)	134	(16.4)	134	(16.4)	
	IIIB	268	(16.4)	134	(16.4)	134	(16.4)	
	IVA	124	(7.6)	62	(7.6)	62	(7.6)	
Platinum cumulative dose, mg	No chemotherapy	481	(29.5)	244	(29.9)	237	(29.1)	0.8911
	< 500 mg	651	(39.9)	326	(40.0)	325	(39.9)	
	≥ 500 mg	498	(30.6)	245	(30.1)	253	(31.0)	
CCI Scores	0	1031	(63.3)	499	(61.2)	532	(65.3)	0.0604
	1	294	(18.0)	148	(18.2)	146	(17.9)	
	≥ 2	305	(18.7)	168	(20.6)	137	(16.8)	
Income	< NT$18,000	469	(28.8)	239	(29.3)	230	(28.2)	0.9623
	NT$18,000-22,500	542	(33.3)	270	(33.1)	272	(33.4)	
	NT$22,500-30,000	257	(15.8)	127	(15.6)	130	(16.0)	
	≥ NT$30,000	362	(22.2)	179	(22.0)	183	(22.5)	
Hospital level	Academic center	961	(59.0)	466	(57.2)	495	(60.7)	0.0957
	Nonacademic center	669	(41.0)	349	(42.8)	320	(39.3)	
Hospital area	North	872	(53.5)	436	(53.5)	436	(53.5)	0.9083
	Middle	331	(20.3)	167	(20.5)	164	(20.1)	
	South	402	(24.7)	198	(24.3)	204	(25.0)	
	East	25	(1.5)	14	(1.7)	11	(1.3)	
RT boost dose, Gy	< 20 Gy	655	(40.2)	309	(37.9)	346	(42.5)	0.0028
	≥ 20 Gy	975	(59.8)	506	(62.1)	469	(57.5)	

EBRT, external beam radiotherapy; RT, radiotherapy; HDR, high dose rate; BT, brachytherapy; IC, intracavitary; CCI, Charlson comorbidity index; RT, radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; mg, milligrams; NT$, new Taiwan dollars.

10-year intervals between the two groups (**Table 1**). Year of diagnosis, pathologic type, FIGO stage, platinum cumulative dose, CCI scores, income, hospital levels, and hospital area were similar in the two cohorts. The matching variables used in this study were age (20-49, 50-59, 60-69, ≥ 70), year of diagnosis, pathologic types, FIGO stages, platinum cumulative dose, CCI score, income, hospital level, and hospital area. *P* values above 0.05 indicated no statistically significant difference in the variables between PSM cohorts (**Table 1**). The

P values of most variables were above 0.5, and the *P* values of age and FIGO stage were close to 1, indicating that the distributions of matching variables were similar. The RT boost dose was not matched because the EBRT boost or HDR boost cumulative total dose and fraction size of RT differed between the two groups (**Table 1**).

Overall survival outcomes between EBRT boost or IC HDR-BT boost

Survival outcomes were significantly different between patients with CC who received contemporary EBRT boost or HDR-BT boost. Multivariate Cox regression analysis revealed that boost modality was a significant predictor of all-cause mortality (**Table 2**). Multivariate Cox regression analyses indicated that HDR-BT-boost was associated with a higher OS than was EBRT boost. The HR in the univariate model was similar to the HR of the multivariate Cox regression analyses. No significant differences were observed in the explanatory variables for patients with CC who received standard WPRT followed by EBRT boost or HDR-BT boost except for boost modality, age, pathologic type, CCI score, concurrent chemoradiotherapy, and FIGO stage (**Table 2**). In the multivariate Cox regression analyses, the AHR (95% confidence intervals [CIs]) for EBRT boost compared with HDR-BT boost was 1.62 (1.43-1.84). The AHRs (95% CI) were 0.88 (0.73-1.05), 1.08 (1.01-1.06), and 1.23 (1.02-1.47) for all-cause mortality among patients aged 50-59, 60-69, and ≥ 70 years compared with those aged 20-49 years, respectively. The AHR of adenocarcinoma was 1.73 (1.49-2.00) compared with that of squamous cell carcinoma, and the AHRs of CCI = 1 and CCI ≥ 2 were 1.25 (1.08-1.45) and 1.53 (1.31-1.78) compared with CCI = 0, respectively. The AHRs (95% CI) for FIGO stages IA2, IB, IIA, IIB, IIIA, IIIB, and IVA compared with FIGO stage IA1 were 1.07 (1.01-1.19), 1.12 (1.03-120), 1.22 (1.13-1.79), 1.28 (1.32-1.88), 2.15 (1.92-2.95), 2.31 (2.10-3.11), and 3.30 (2.62-4.16), respectively. The AHRs (95% CI) of concurrent chemoradiotherapy were 0.62 (0.53-0.72) and 0.59 (0.50-0.69) for all-cause mortality among patients with a platinum cumulative dose of < 500 and ≥ 500 mg compared with those who did not receive chemotherapy (RT alone), respectively.

Overall survival outcomes stratified by FIGO stage

Multivariate Cox regression analysis revealed that HDR-BT boost was associated with a significantly higher OS compared with EBRT boost with FIGO stages I-III after stratification of patients with CC with FIGO stages I, IIA, IIB, III, and IVA (**Table 3**). The AHRs of all-cause mortality for EBRT boost compared with HDR-BT boost were 1.94 (1.30-2.89), 1.81 (1.23-2.91), 1.80 (1.37-2.38), 1.44 (1.14-1.81), and 1.08 (0.67-1.73) in patients with CC with FIGO stages I, IIA, IIB, III, and IVA, respectively (**Table 3**). However, no significant difference in the all-cause mortality of patients with CC with FIGO stage IVA was observed between those who received EBRT boost and those who received HDR-BT boost. Among the patients with CC with FIGO stages IIA, IIB, III, or IVA, those who received concurrent chemoradiotherapy had a greater OS than those who received no chemotherapy (**Table 3**). No statistically significant difference in all-cause mortality among patients with FIGO stage I was observed between those who received concurrent chemoradiotherapy and those who received RT alone. The other independent poor prognostic factors of all-cause mortality were adenocarcinoma, no chemotherapy in FIGO stages II-IVA, age ≥ 70 years, and CCI ≥ 2 in patients with CC who received standard WPRT followed by RT boost (**Table 3**).

Kaplan-Meier method for propensity score-matched cohorts

Figure 1 displays survival curves for all-cause mortality obtained using the Kaplan-Meier method for the PSM cohort of patients with CC who received standard WPRT, followed by different RT boost modalities, stratified by all FIGO stages (stages I, IIA, IIB, III, and IVA). The OS curve for HDR-BT boost was higher than that for EBRT boost in patients with CC with FIGO stages I-IVA who received WPRT ($P < 0.0001$). The OS curves for HDR-BT boost were higher than that for EBRT boost in FIGO stages I, IIA, IIB, and III (*P* values of 0.0007, 0.0196, < 0.0001, and 0.0004, respectively). The OS curve was not statistically significant between EBRT boost and HDR-BT boost in patients with CC with FIGO stage IVA ($P = 0.2598$).

Table 2. Cox proportional-hazards regression analysis of the risk of all-cause mortality among patients with cervical cancer who received EBRT boost or IC HDR-BT boost

Variable		Univariate			Multivariate		
		HR	95% CI	*P* value	AHR	95% CI	*P* value
RT boost modality	IC HDR-BT boost	1.00		< 0.0001	1.00		< 0.0001
	EBRT boost	2.30	(2.06-2.57)		1.62	(1.43-1.84)	
Pathologic type	SCC	1.00		< 0.0001	1.00		< 0.0001
	Adenocarcinoma	1.52	(1.31-1.75)		1.73	(1.49-2.00)	
FIGO stage	IA1	1.00		< 0.0001	1.00		< 0.0001
	IA2	1.11	(1.00-1.22)		1.07	(1.01-1.19)	
	IB	1.19	(1.02-1.32)		1.12	(1.03-1.20)	
	IIA	1.27	(1.09-1.71)		1.22	(1.13-1.79)	
	IIB	1.33	(1.04-1.46)		1.28	(1.32-1.88)	
	IIIA	2.27	(1.92-2.69)		2.15	(1.92-2.95)	
	IIIB	2.54	(1.99-2.88)		2.31	(2.10-3.11)	
	IVA	3.44	(2.76-4.29)		3.30	(2.62-4.16)	
RT boost dose	< 20 Gy	1.00		< 0.1264	1.00		0.1503
	≥ 20 Gy	1.15	(0.81-1.51)		1.13	(0.90-1.39)	
Platinum cumulative dose	No chemotherapy	1.00		< 0.0001	1.00		< 0.0001
	< 500 mg	0.48	(0.42-0.55)	< 500 mg	0.62	(0.53-0.72)	
	≥ 500 mg	0.45	(0.39-0.52)		0.59	(0.50-0.69)	
Age	20-49	1.00		< 0.0001	1.00		< 0.0001
	50-59	0.93	(0.78-1.10)		0.88	(0.73-1.05)	
	60-69	1.10	(1.01-1.19)		1.08	(1.01-1.06)	
	≥ 70	1.96	(1.68-2.28)		1.23	(1.02-1.47)	
Year of diagnosis	2008-2010	1.00		0.2790	1.00		0.2941
	2011-2013	1.08	(0.95-1.23)		0.96	(0.85-1.10)	
	2014-2016	0.97	(0.83-1.13)		0.88	(0.75-1.03)	
CCI score	0	1.00		< 0.0001	1.00		< 0.0001
	1	1.50	(1.30-1.72)		1.25	(1.08-1.45)	
	≥ 2	2.17	(1.89-2.48)		1.53	(1.31-1.78)	
Income	< NT$18,000	1.00		0.0658	1.00		0.1019
	NT$18,000-22,500	0.89	(0.77-1.02)		0.84	(0.73-1.07)	
	NT$22,500-30,000	0.88	(0.74-1.05)		0.97	(0.81-1.16)	
	≥ NT$30,000	0.82	(0.70-1.05)		0.93	(0.80-1.09)	
Hospital level	Academic centers	1.00		< 0.0001	1.00		0.1534
	Nonacademic centers	1.33	(1.19-1.49)		1.09	(0.97-1.23)	
Hospital area	North	1.00		0.1419	1.00		0.2272
	Middle	1.03	(0.90-1.17)		1.10	(0.96-1.26)	
	South/East	1.15	(1.00-1.31)		1.11	(0.97-1.28)	

EBRT, external beam radiotherapy; HDR, high dose rate; BT, brachytherapy; IC, intracavitary; CCI, Charlson comorbidity index; RT, radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; mg, milligrams; NT$, new Taiwan dollar; AHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; *All of the aforementioned variables were used in the multivariate analysis.

Different contemporary EBRT techniques and boost

The AHRs of all-cause mortality for the PSM cohorts, stratified according to RT technique (IMRT or VMAT) and total cumulative boost dosage (< 20 or ≥ 20 Gy boost), are displayed in Supplementary Figure 1. The OS of patients with CC who received WPRT followed by HDR-BT boost was significantly higher for overall, I, IIA, IIB, and III FIGO clinical stages (Supplementary Figure 1). The OS of IMRT boost or VMAT boost was inferior to that of HDR-BT boost for all FIGO stages. The OS of patients with FIGO stages I and IIA who received a boost dose of < 20 Gy was not significantly

Table 3. Cox proportional-hazards regression analysis of the risk of all-cause mortality, stratified by FIGO stage

Variable		Stage I			Stage IIA			Stage IIB			Stage III			Stage IVA		
		AHR	95% CI	*P* value	AHR	95% CI	*P* value	AHR	95% CI	*P* value	AHR	95% CI	*P* value	AHR	95% CI	*P* value
RT boost modality	IC HDR-BT boost	1.00		0.0004	1.00		0.0029	1.00		< 0.0001	1.00		0.0001	1.00		0.2713
	EBRT boost	1.94	(1.30-2.89)		1.81	(1.23-2.91)		1.80	(1.37-2.38)		1.44	(1.14-1.81)		1.08	(0.67-1.73)	
Pathologic type	SCC	1.00		0.0372	1.00		0.0733	1.00		< 0.0001	1.00		0.0009	1.00		0.0397
	Adenocarcinoma	1.46	(1.02-2.08)		1.66	(0.95-2.90)		2.01	(1.56-2.60)		1.62	(1.22-2.15)		1.66	(1.02-2.68)	
RT boost dose	< 20 Gy	1.00		0.0595	1.00		0.0783	1.00		0.2650	1.00		0.1694	1.00		0.0699
	≥ 20 Gy	1.41	(0.99-2.02)		1.43	(0.96-2.11)		1.13	(0.91-1.40)		1.15	(0.94-1.41)		1.44	(0.97-2.13)	
Platinum cumulative dose	No chemotherapy	1.00		0.2316	1.00		0.0085	1.00		0.0136	1.00		< 0.0001	1.00		0.0035
	< 500 mg	0.71	(0.48-1.06)		0.49	(0.29-0.81)		0.68	(0.51-0.89)		0.57	(0.44-0.74)		0.60	(0.37-0.97)	
	≥ 500 mg	0.79	(0.52-1.19)		0.52	(0.31-0.86)		0.67	(0.49-0.92)		0.56	(0.43-0.74)		0.38	(0.22-0.67)	
Age	20-49	1.00		0.1522	1.00		0.1320	1.00		< 0.0001	1.00		0.0058	1.00		0.0042
	50-59	1.22	(0.75-1.98)		1.09	(0.57-2.10)		0.86	(0.63-1.18)		0.71	(0.53-0.96)		0.98	(0.48-2.02)	
	60-69	1.17	(0.67-2.03)		0.70	(0.35-1.39)		0.69	(0.48-1.02)		0.71	(0.51-1.09)		0.86	(0.41-1.79)	
	≥ 70	1.66	(1.03-2.68)		1.47	(1.15-1.69)		1.37	(1.06-1.84)		1.24	(1.16-1.41)		1.17	(1.05-2.13)	
Year of diagnosis	2008-2010	1.00		0.5574	1.00		0.4280	1.00		0.8723	1.00		0.9666	1.00		0.0607
	2011-2013	0.95	(0.67-1.34)		0.82	(0.52-1.28)		1.02	(0.81-1.30)		1.02	(0.82-1.28)		0.70	(0.45-1.07)	
	2014-2016	0.79	(0.51-1.23)		0.69	(0.39-1.22)		0.95	(0.71-1.28)		1.04	(0.80-1.35)		0.53	(0.31-0.92)	
CCI score	0	1.00		0.0006	1.00		0.0064	1.00		0.0009	1.00		0.0544	1.00		0.0380
	1	1.17	(0.78-1.74)		1.49	(0.92-2.41)		1.15	(0.88-1.51)		1.25	(0.96-1.63)		1.38	(0.83-2.31)	
	≥ 2	2.05	(1.41-2.98)		2.06	(1.31-3.24)		1.71	(1.29-2.26)		1.23	(1.13-1.61)		1.14	(1.09-2.32)	
Income	< NT$18,000	1.00		0.9812	1.00		0.2621	1.00		0.0777	1.00		0.4510	1.00		0.2693
	NT$18,000-22,500	1.08	(0.74-1.56)		0.92	(0.59-1.46)		0.72	(0.56-1.3)		0.86	(0.68-1.09)		0.66	(0.42-1.05)	
	NT$22,500-30,000	1.02	(0.63-1.64)		1.45	(0.82-2.56)		0.75	(0.52-1.09)		1.07	(0.79-1.44)		0.79	(0.42-1.49)	
	≥ NT$30,000	1.07	(0.69-1.64)		0.78	(0.43-1.43)		0.86	(0.66-1.13)		0.91	(0.70-1.19)		1.03	(0.62-1.71)	
Hospital level	Academic center	1.00		0.1709	1.00		0.6078	1.00		0.8042	1.00		0.2065	1.00		0.8170
	Nonacademic centers	1.25	(0.91-1.73)		0.90	(0.62-1.33)		1.03	(0.83-1.27)		1.14	(0.93-1.39)		1.05	(0.71-1.54)	
Hospital area	North	1.00		0.5646	1.00		0.4673	1.00		0.2864	1.00		0.8413	1.00		0.3926
	Middle	0.88	(0.61-1.27)		0.84	(0.54-1.31)		1.19	(0.94-1.50)		1.07	(0.85-1.35)		1.44	(0.85-2.46)	
	South/East	1.10	(0.77-1.57)		1.17	(0.73-1.86)		1.15	(0.88-1.50)		1.04	(0.82-1.33)		1.17	(0.75-1.81)	

EBRT, external beam radiotherapy; HDR, high dose rate; BT, brachytherapy; IC, intracavitary; CCI, Charlson comorbidity index; RT, radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; mg, milligrams; NT$, new Taiwan dollars; AHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio. *All of the aforementioned variables were used in the multivariate analysis.

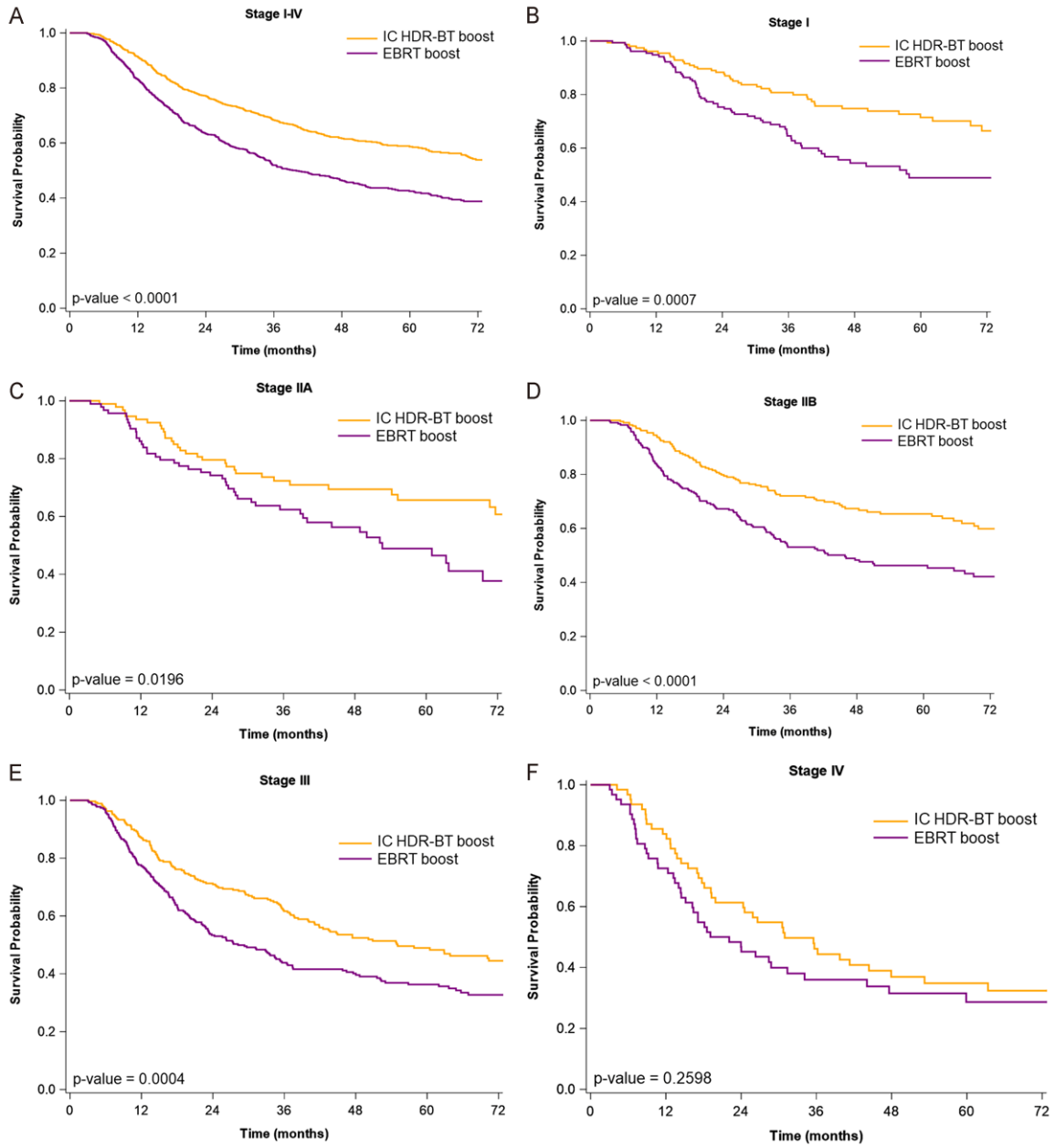


Figure 1. Survival curves of all-cause mortality obtained using the Kaplan-Meier method for propensity score-matched cohorts at (A) stages I-IV, (B) stage I, (C) stage IIA, (D) stage IIB, (E) stage III, and (F) stage IVA.

different between those who received EBRT boost and those who received HDR-BT boost (Supplementary Figure 1).

Discussion

Boost techniques with BT or contemporary EBRT techniques are expected to provide a higher dose of RT to the cervix while sparing the surrounding normal tissue. The value of BT boost was demonstrated in a 2013 study of over 7,000 women with stage IB2 to IVA CC identified from the Surveillance, Epidemiology, and End Results database [13]. A matched cohort analysis of patients treated between 2000 and 2009 revealed that the use of BT boost resulted in significantly higher rates of cancer-specific survival (64% versus 52%) and OS (58% versus 46%) after 4 years. However, the aforementioned study also revealed a decrease in the use of BT between 1998 and 2009 from 83% to 58%. This decrease in use

was observed regardless of stage and histologic type [13]. The use of boost appears to be crucial in patients with CC, with BT boost displaying superior OS compared with no BT boost and no difference compared with contemporary EBRT boost [13].

Another population-based study involved the analysis of data from the National Cancer Database of 7,654 patients treated between January 2004 and December 2011 with advanced FIGO stages IIB to IVA cervical carcinoma [25]. Gill et al. reported a decrease in the use of BT for the curative treatment of CC from 97% in 2004 to 86% in 2011 [25]. They further reported that the use of advanced technologies, such as IMRT or SBRT, for boost increased from 3.3% to 14% over the same period [25]. Multivariable survival analysis revealed that using IMRT boost or SBRT boost resulted in inferior OS compared with brachytherapy (HR: 1.86). This lower survival also occurred with a higher HR compared with the survival decrease when chemotherapy was not administered (HR: 1.56) [25]. However, Gill et al. only investigated patients with CC in advanced stages (IIB-IVA), and more than 50% of patients had stage IIIB-IVA CC. Therefore, the findings could not be extrapolated to early stages or all stages [25]. Moreover, their study did not include a head-to-head PSM cohort study design, and thus numerous clinical characteristics were significantly inhomogeneous between the IMRT/SBRT boost and BT boost groups [25]. Furthermore, most of the included patients were Caucasian, with scarcely any Asian patients [25]. The biologically effective dose (BED) differs considerably.

IMRT and SBRT [46, 47] and the combination of IMRT and SBRT used in the study by Gill et al. may be unsuitable. Furthermore, LDR-BT is a common type of BT in the United States and European countries [48]. Gill et al. did not describe the BT equipment used for HDR and LDR-BT boost [25]. The EBRT boost modalities in their study differed from the standard RT fraction size boost with IMRT/VMAT boost used in our study [25]. The BT boost modalities were unclear in the study by Gill et al., whereas ours were all HDR-BT boost. We aimed to answer the research questions using homogeneous techniques and a standard radiation fraction size for comparing contemporary EBRT boost with HDR-BT boost.

HDR-BT and LDR-BT are valuable options for dose escalation when used in conjunction with EBRT for men with intermediate-risk, localized prostate cancer [49]. Research on RT dose escalation in prostate cancer has indicated that in addition to BT boost, IMRT with dose escalation seems to be a reasonable and feasible treatment for patients with prostate cancer [1]. RT dose escalation improved the 5-year biochemical control rate for the intermediate-risk prostate cancer group. IMRT led to lower acute and late genitourinary side effects compared with BT boost [1]. IMRT enabled further dose escalation and exhibited lower GI side effects among prostate cancer patients compared with BT boost [1]. The dosimetric results were similar for IMRT and VMAT in patients with CC [50]. IMRT/VMAT boost would thus be expected to achieve favorable outcomes. Therefore, we administered IMRT and VMAT in the same group (**Table 1**). Although a comparative study investigated standard RT fraction size with IMRT boost and BT boost in pelvic malignancies, such as prostate cancer [1], no comparative study has assessed standard RT fraction size with IMRT boost and BT boost in patients with CC. Our study is the first to estimate the effects of IMRT/VMAT boost and HDR-BT boost in patients with CC.

As indicated in **Table 1**, all covariates in our PSM cohorts were balanced between the EBRT boost and BT boost groups. The multivariable analysis presented in **Table 2** indicates that the independent poor prognostic factors of all-cause mortality are adenocarcinoma, no chemotherapy, CCI score ≥ 1, age ≥ 60 years, and advanced FIGO stage for patients with CC. Some independent poor prognostic factors of all-cause mortality were determined to be no chemotherapy, old age, high CCI score, advanced FIGO stage, and EBRT boost, which accorded with the results reported by Gill et al. [25]. However, the study by Gill et al. involved various CC histologies, and they did not report adenocarcinomas [25]. Our study revealed that adenocarcinomas are a poor independent prognostic factor for patients with CC who received RT, which accords with the results of other studies [26, 27, 51]. Our study revealed that cumulative total doses of platinum are proportional to OS, especially in patients with FIGO stage IV (**Tables 2** and **3**). Gill et al. did not report chemotherapy regimens or doses [25]. FIGO stage has a significant effect on OS (**Table**

2); thus, stratification by FIGO stage was performed, as presented in **Table 3**. The survival effects of EBRT boost and HDR-BT boost could be differentiated between different FIGO stages (**Table 3**). However, the survival effects of EBRT boost and BT boost could not be differentiated between different FIGO stages in the study by Gill et al. [25].

Multivariate analysis stratified by FIGO stage revealed that the independent prognostic factors of all-cause mortality were mostly similar in all stages (**Tables 2** and **3**). The only difference was "no chemotherapy", which was not a statistically significant prognostic factor for all-cause mortality in patients with FIGO stage I. Although some experts prefer concurrent chemoradiotherapy in these patients with CC, whether the benefits of concurrent chemoradiotherapy outweigh the increased morbidity of treatment in women with stage I cervical cancer has not been determined. As presented in **Table 3**, we demonstrated that concurrent chemoradiotherapy did not have survival benefits in patients with FIGO stage I CC who received RT. Therefore, RT alone may suffice for FIGO stage I CC. Furthermore, the other independent prognostic factors of all-cause mortality in FIGO stage I were similar in all stages (**Table 2**). Poor prognostic factors of all-cause mortality included adenocarcinoma, age ≥ 70 years, and CCI score ≥ 2 (**Table 3**). Furthermore, nonsignificant survival differences in patients with FIGO stage IVA CC were observed between those treated with EBRT boost and those treated with HDR-BT boost (**Table 3** and **Figure 1**). Primary concurrent chemoradiotherapy should be provided for women with locally advanced CC [52]. The benefits of treatment are higher among women with earlier stages compared with more advanced stage [53, 54]. The nonsignificant difference in survival after EBRT boost and HDR-BT boost may be partially caused by incomplete eradication of most of the tumor burden in FIGO stage IVA CC after standard WPRT with either EBRT boost or HDR-BT boost, resulting in a lack of significant survival benefits from HDR-BT boost among patients with stage IVA CC (**Table 3**). Moreover, tumors of FIGO stage IVA may display a wide-ranging field extension beyond the isodose curve of HDR-BT boost. Therefore, FIGO stage IVA CC could not be eradicated by HDR-BT boost.

This is the first study to report the AHRs of all-cause mortality for PSM cohorts, stratified by different contemporary EBRT techniques (IMRT or VMAT) and boost dosages (< or ≥ 20 Gy), as displayed in Supplementary Figure 1. Survival was higher when HDR-BT boost was used than when either IMRT boost or VMAT boost EBRT was used, which may be because of the insufficient irradiation BED for eradicating CC using EBRT boost compared with HDR-BT boost [55]. Stratification of the boost dosage revealed that at a dose of ≥ 20 Gy, the survival rate was higher for HDR-BT boost than for EBRT boost for patients with CC in all FIGO stages (I, IIA, IIB, III, and IVA). However, no significant survival differences were observed between EBRT boost and HDR-BT boost in patients with CC with FIGO stage I or IIA for boost doses of < 20 Gy. This lack of a significant difference in FIGO stages I-IIA (early-stage CC) may be because the relatively small tumor burden of early-stage CC could be eradicated by WPRT followed by EBRT boost or HDR-BT boost (Supplementary Figure 1). Our findings indicate that WPRT followed by EBRT boost could be considered an alternative boost choice for early-stage CC (FIGO stages I-IIA) if BT equipment is limited.

The strengths of this study are its large sample size and the consistent covariates of the CC population after PSM. We achieved balanced clinical characteristics between the EBRT boost and HDR-BT boost groups. Most major covariates (age, year of diagnosis, pathologic type, FIGO stage, RT boost dose, platinum cumulative dose, CCI score, income, hospital level, and hospital area) were considered in the PSM analysis. The present study is the first head-to-head PSM study to estimate the effect of EBRT boost and HDR-BT boost on survival among patients with CC who received standard WPRT. HDR-BT boost exhibited greater survival compared with EBRT boost for CC treatment in all FIGO stages, except stage IVA (**Table 3** and **Figure 1**). These findings should be considered in future clinical practice and prospective clinical trials.

This study has some limitations. First, all patients with CC were enrolled from an Asian population, and the effect of ethnic susceptibility remains unclear; therefore, caution should be exercised when extrapolating our results to non-Asian populations. Second, the diagnoses of all comorbid conditions were based on

ICD-9-CM codes. However, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of the diagnoses, and hospitals with outlier charges or practices may be audited and heavily penalized if malpractice or discrepancies are identified. A large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential for obtaining crucial information on population specificity and disease occurrence. Third, there is no comparative study until now for different side effects from contemporary EBRT and HDR-BT boost in CC patients. In our study, the side effects of contemporary EBRT and HDR-BT boost were not recorded in the TCRD. Thus, we could not analyze the side effects of different techniques of irradiation boost. However, the irradiation courses were completed with sufficient irradiation dose in the enrolled patients, there was no potential bias for treatment toxicity contributed to all-cause death. Therefore, our conclusion could not be overturned. Finally, the Cancer Registry database does not contain information regarding dietary habits, socioeconomic status, or body mass index, all of which may be risk factors for mortality. However, the magnitude and statistical significance of the observed effects in this study suggest that these limitations are unlikely to have affected the conclusions.

Conclusions

BT boost should be the first choice of RT boost instead of EBRT boost for patients with CC, regardless of whether they have received IMRT boost or VMAT boost.

Acknowledgements

Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Number: 10908, 10909, 11001, 11002, 11003, 11006, and 11013). Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201702019).

Disclosure of conflict of interest

None.

Abbreviations

EBRT, external beam radiotherapy; CC, cervical cancer; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; HDR, high dose rate; BT, brachytherapy; PSM, propensity score matching; AHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; CCI, Charlson comorbidity index; RT, radiotherapy; LDR, low dose rate; TCRD, Taiwan Cancer Registry Database; WPRT, whole-pelvis radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; SBRT, stereotactic body radiation therapy; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; OS, overall survival; BED, biologically effective dose.

Address correspondence to: Dr. Szu-Yuan Wu, Division of Radiation Oncology, Department of Medicine, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, No. 83, Nanchang Street, Luodong Township, Yilan County 265, Taiwan. E-mail: szuyuanwu5399@gmail.com

References

[1] Wong WW, Vora SA, Schild SE, Ezzell GA, Andrews PE, Ferrigni RG and Swanson SK. Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. Cancer 2009; 115: 5596-5606.

[2] Teoh M, Clark CH, Wood K, Whitaker S and Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol 2011; 84: 967-996.

[3] Sethi RA, Jozsef G, Grew D, Marciscano A, Pennell R, Babcock M, McCarthy A, Curtin J and Schiff PB. Is there a role for an external beam boost in cervical cancer radiotherapy? Front Oncol 2013; 3: 3.

[4] Mahmoud O, Kilic S, Khan AJ, Beriwal S and Small W Jr. External beam techniques to boost cervical cancer when brachytherapy is not an option-theories and applications. Ann Transl Med 2017; 5: 207.

[5] Health Promotion Administration MoHaW. Taiwan cancer registry annual report. 2017.

[6] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.

[7] Medhin LB, Tekle LA, Achila OO and Said S. Incidence of cervical, ovarian and uterine cancer in eritrea: data from the national health laboratory, 2011-2017. Sci Rep 2020; 10: 9099.

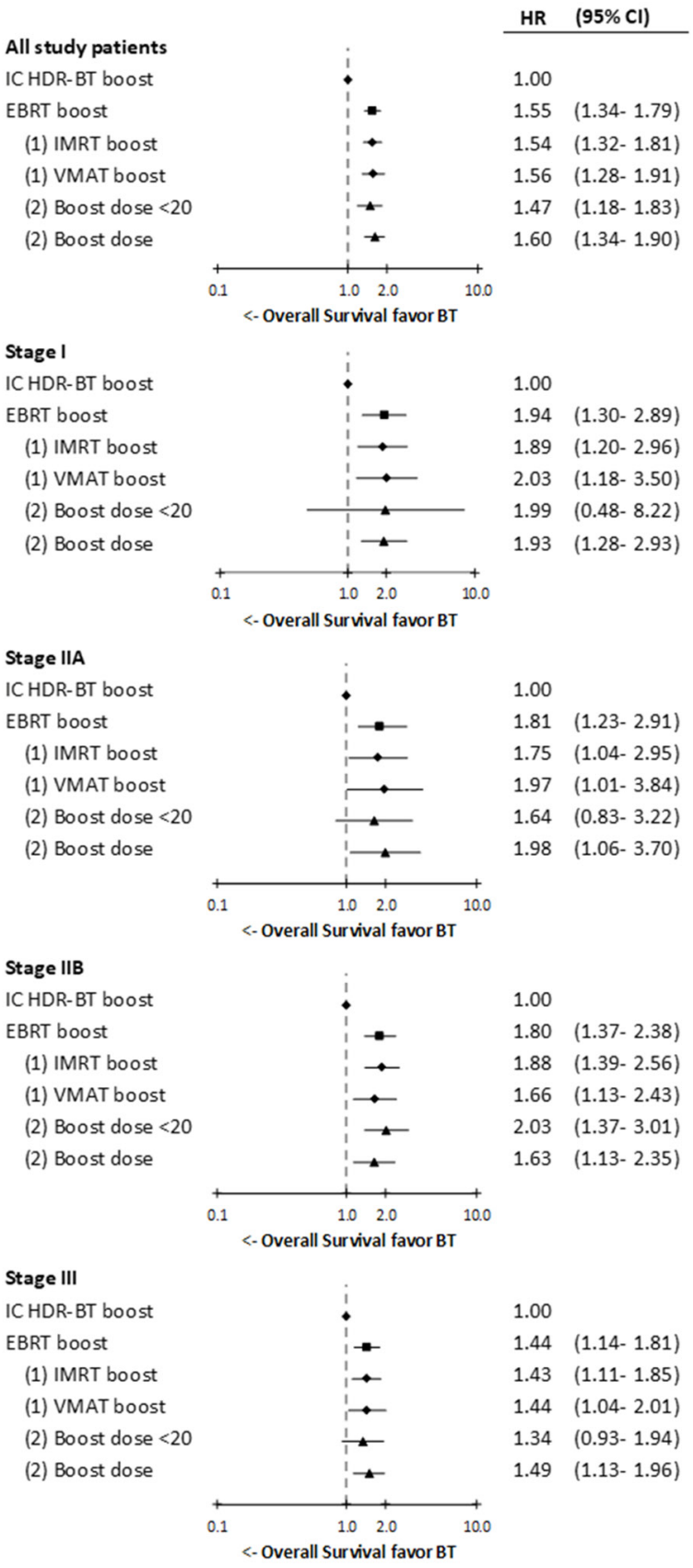
[8] Denny L, Herrero R, Levin C and Kim JJ. Cervical Cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer: disease control priorities, third edition (Volume 3). Washington (DC): 2015.

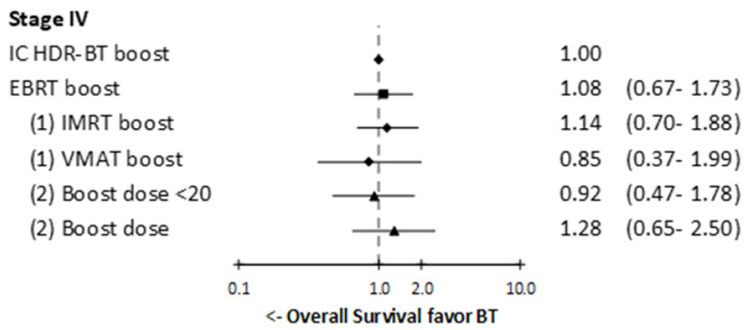
[9] Maine D, Hurlburt S and Greeson D. Cervical cancer prevention in the 21st century: cost is

not the only issue. Am J Public Health 2011; 101: 1549-1555.
[10] Mahvi DA, Liu R, Grinstaff MW, Colson YL and Raut CP. Local cancer recurrence: the realities, challenges, and opportunities for new therapies. CA Cancer J Clin 2018; 68: 488-505.
[11] Wang N, Guan QL, Wang K, Zhou X, Gao C, Yang HT and Ni TG. Radiochemotherapy versus radiotherapy in locally advanced cervical cancer: a meta-analysis. Arch Gynecol Obstet 2011; 283: 103-108.
[12] Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, Favini G, Ferri L and Mangioni C. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997; 350: 535-540.
[13] Han K, Milosevic M, Fyles A, Pintilie M and Viswanathan AN. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 2013; 87: 111-119.
[14] Eifel PJ, Moughan J, Erickson B, Iarocci T, Grant D and Owen J. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. Int J Radiat Oncol Biol Phys 2004; 60: 1144-1153.
[15] Eifel PJ, Ho A, Khalid N, Erickson B and Owen J. Patterns of radiation therapy practice for patients treated for intact cervical cancer in 2005 to 2007: a quality research in radiation oncology study. Int J Radiat Oncol Biol Phys 2014; 89: 249-256.
[16] Petereit DG, Sarkaria JN, Potter DM and Schink JC. High-dose-rate versus low-dose-rate brachytherapy in the treatment of cervical cancer: analysis of tumor recurrence--the University of Wisconsin experience. Int J Radiat Oncol Biol Phys 1999; 45: 1267-1274.
[17] Lertsanguansinchai P, Lertbutsayanukul C, Shotelersuk K, Khorprasert C, Rojpornpradit P, Chottetanaprasith T, Srisuthep A, Suriyapee S, Jumpangern C, Tresukosol D and Charoonsantikul C. Phase III randomized trial comparing LDR and HDR brachytherapy in treatment of cervical carcinoma. Int J Radiat Oncol Biol Phys 2004; 59: 1424-1431.
[18] Hareyama M, Sakata K, Oouchi A, Nagakura H, Shido M, Someya M and Koito K. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. Cancer 2002; 94: 117-124.
[19] Falkenberg E, Kim RY, Meleth S, De Los Santos J and Spencer S. Low-dose-rate vs. high-dose-rate intracavitary brachytherapy for carcinoma of the cervix: The University of Alabama at Birmingham (UAB) experience. Brachytherapy 2006; 5: 49-55.
[20] Parker K, Gallop-Evans E, Hanna L and Adams M. Five years' experience treating locally advanced cervical cancer with concurrent chemoradiotherapy and high-dose-rate brachytherapy: results from a single institution. Int J Radiat Oncol Biol Phys 2009; 74: 140-146.
[21] Hellebust TP, Kristensen GB and Olsen DR. Late effects after radiotherapy for locally advanced cervical cancer: comparison of two brachytherapy schedules and effect of dose delivered weekly. Int J Radiat Oncol Biol Phys 2010; 76: 713-718.
[22] Liu R, Wang X, Tian JH, Yang K, Wang J, Jiang L and Hao XY. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer. Cochrane Database Syst Rev 2014; CD007563.
[23] Kirisits C, Rivard MJ, Baltas D, Ballester F, De Brabandere M, van der Laarse R, Niatsetski Y, Papagiannis P, Hellebust TP, Perez-Calatayud J, Tanderup K, Venselaar JL and Siebert FA. Review of clinical brachytherapy uncertainties: analysis guidelines of GEC-ESTRO and the AAPM. Radiother Oncol 2014; 110: 199-212.
[24] Lin SM, Ku HY, Chang TC, Liu TW, Chang CS and Hong JH. Outcomes for cervical cancer patients treated with radiation in high-volume and low-volume hospitals. Int J Radiat Oncol Biol Phys 2018; 102: 184-193.
[25] Gill BS, Lin JF, Krivak TC, Sukumvanich P, Laskey RA, Ross MS, Lesnock JL and Beriwal S. National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements. Int J Radiat Oncol Biol Phys 2014; 90: 1083-1090.
[26] Zhang J, Qin L, Chen HM, Hsu HC, Chuang CC, Chen D and Wu SY. Outcome patterns of cervical adenocarcinoma and squamous cell carcinoma following curative surgery: before and after propensity score matching analysis of a cohort study. Am J Cancer Res 2020; 10: 1793-1807.
[27] Zhang J, Qin L, Chen HM, Hsu HC, Chuang CC, Chen D and Wu SY. Overall survival, locoregional recurrence, and distant metastasis of definitive concurrent chemoradiotherapy for cervical squamous cell carcinoma and adenocarcinoma: before and after propensity score matching analysis of a cohort study. Am J Cancer Res 2020; 10: 1808-1820.
[28] Liu WC, Liu HE, Kao YW, Qin L, Lin KC, Fang CY, Tsai LL, Shia BC and Wu SY. Definitive radiotherapy or surgery for early oral squamous cell carcinoma in old and very old patients: a propensity-score-matched, nationwide, population-based cohort study. Radiother Oncol 2020; 151: 214-221.
[29] Lin KC, Chen TM, Yuan KS, Wu ATH and Wu SY. Assessment of predictive scoring system for 90-day mortality among patients with locally

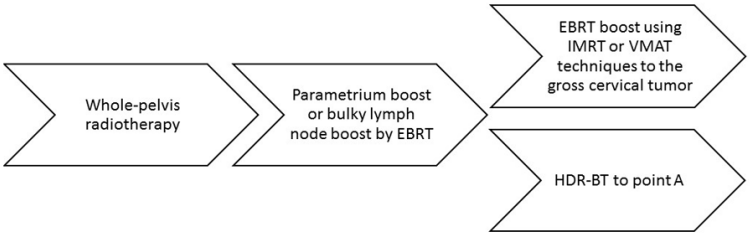
advanced head and neck squamous cell carcinoma who have completed concurrent chemoradiotherapy. JAMA Netw Open 2020; 3: e1920671.
[30] Lin YK, Hsieh MC, Wang WW, Lin YC, Chang WW, Chang CL, Cheng YF and Wu SY. Outcomes of adjuvant treatments for resectable intrahepatic cholangiocarcinoma: chemotherapy alone, sequential chemoradiotherapy, or concurrent chemoradiotherapy. Radiother Oncol 2018; 128: 575-583.
[31] Lin YK, Hsieh MC, Chang CL, Chow JM, Yuan KS, Wu ATH and Wu SY. Intensity-modulated radiotherapy with systemic chemotherapy improves survival in patients with nonmetastatic unresectable pancreatic adenocarcinoma: a propensity score-matched, nationwide, population-based cohort study. Radiother Oncol 2018; 129: 326-332.
[32] Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM and Wu SY. Treatment outcomes for unresectable intrahepatic cholangiocarcinoma: nationwide, population-based, cohort study based on propensity score matching with the Mahalanobis metric. Radiother Oncol 2018; 129: 284-292.
[33] Yen YC, Chang JH, Lin WC, Chiou JF, Chang YC, Chang CL, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Effectiveness of esophagectomy in patients with thoracic esophageal squamous cell carcinoma receiving definitive radiotherapy or concurrent chemoradiotherapy through intensity-modulated radiation therapy techniques. Cancer 2017; 123: 2043-2053.
[34] Lin WC, Ding YF, Hsu HL, Chang JH, Yuan KS, Wu ATH, Chow JM, Chang CL, Chen SU and Wu SY. Value and application of trimodality therapy or definitive concurrent chemoradiotherapy in thoracic esophageal squamous cell carcinoma. Cancer 2017; 123: 3904-3915.
[35] Chen TM, Lin KC, Yuan KS, Chang CL, Chow JM and Wu SY. Treatment of advanced nasopharyngeal cancer using low- or high-dose concurrent chemoradiotherapy with intensity-modulated radiotherapy: a propensity score-matched, nationwide, population-based cohort study. Radiother Oncol 2017; 129: 23-29.
[36] Chassagne D, Dutreix A, Almond P, Burgers JMV, Busch M and Joslin CA. International Commission of Radiation Units and Measurements. Dose and Volume Specification for Reporting Intracavitary Therapy in Gynaecology. Bethesda, MD: ICRU; 1985; International Commission of Radiation Units and Measurements: Bethesda, 1 March 1985, 1985; p NP.
[37] Viswanathan AN and Thomadsen B; American Brachytherapy Society Cervical Cancer Recommendations Committee; American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. Brachytherapy 2012; 11: 33-46.
[38] NCCN Clinical Practice Guidelines in Oncology. Available online: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed on 21 May 2020).
[39] Bahreini F, Soltanian AR and Mehdipour P. A meta-analysis on concordance between immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) to detect HER2 gene overexpression in breast cancer. Breast Cancer 2015; 22: 615-625.
[40] Charlson M, Szatrowski TP, Peterson J and Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47: 1245-1251.
[41] Chen JH, Yen YC, Yang HC, Liu SH, Yuan SP, Wu LL, Lee FP, Lin KC, Lai MT, Wu CC, Chen TM, Chang CL, Chow JM, Ding YF and Wu SY. Curative-intent aggressive treatment improves survival in elderly patients with locally advanced head and neck squamous cell carcinoma and high comorbidity index. Medicine (Baltimore) 2016; 95: e3268.
[42] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150-161.
[43] D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998; 17: 2265-2281.
[44] Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 2013; 32: 2837-2849.
[45] Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med 2014; 33: 1242-1258.
[46] Jones B, Dale RG, Deehan C, Hopkins KI and Morgan DA. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol (R Coll Radiol) 2001; 13: 71-81.
[47] Brown JM, Carlson DJ and Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys 2014; 88: 254-262.
[48] Skowronek J. Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer - between options. J Contemp Brachytherapy 2013; 5: 33-41.
[49] Zaorsky NG, Davis BJ, Nguyen PL, Showalter TN, Hoskin PJ, Yoshioka Y, Morton GC and Horwitz EM. The evolution of brachytherapy for prostate cancer. Nat Rev Urol 2017; 14: 415-439.

[50] Sharfo AW, Voet PW, Breedveld S, Mens JW, Hoogeman MS and Heijmen BJ. Comparison of VMAT and IMRT strategies for cervical cancer patients using automated planning. Radiother Oncol 2015; 114: 395-401.
[51] Wu SY, Huang EY and Lin H. Optimal treatments for cervical adenocarcinoma. Am J Cancer Res 2019; 9: 1224-1234.
[52] Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, Chon HS, Chu C, Clark R, Cohn D, Crispens MA, Damast S, Dorigo O, Eifel PJ, Fisher CM, Frederick P, Gaffney DK, Han E, Huh WK, Lurain JR, Mariani A, Mutch D, Nagel C, Nekhlyudov L, Fader AN, Remmenga SW, Reynolds RK, Tillmanns T, Ueda S, Wyse E, Yashar CM, McMillian NR and Scavone JL. Cervical cancer, version 3. 2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019; 17: 64-84.
[53] Yamashita H, Okuma K, Kawana K, Nakagawa S, Oda K, Yano T, Kobayashi S, Wakui R, Ohtomo K and Nakagawa K. Comparison between conventional surgery plus postoperative adjuvant radiotherapy and concurrent chemoradiation for FIGO stage IIB cervical carcinoma: a retrospective study. Am J Clin Oncol 2010; 33: 583-586.
[54] Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev 2010; 2010: CD008285.
[55] Sharma BA, Singh TT, Singh LJ, Singh YI and Devi YS. Biological effective doses in the intracavitary high dose rate brachytherapy of cervical cancer. J Contemp Brachytherapy 2011; 3: 188-192.


HR (95% CI)
All study patients
IC HDR-BT boost 1.00
EBRT boost 1.55 (1.34- 1.79)
(1) IMRT boost 1.54 (1.32- 1.81)
(1) VMAT boost 1.56 (1.28- 1.91)
(2) Boost dose <20 1.47 (1.18- 1.83)
(2) Boost dose 1.60 (1.34- 1.90)
0.1 1.0 2.0 10.0
<- Overall Survival favor BT
Stage I
IC HDR-BT boost 1.00
EBRT boost 1.94 (1.30- 2.89)
(1) IMRT boost 1.89 (1.20- 2.96)
(1) VMAT boost 2.03 (1.18- 3.50)
(2) Boost dose <20 1.99 (0.48- 8.22)
(2) Boost dose 1.93 (1.28- 2.93)
0.1 1.0 2.0 10.0
<- Overall Survival favor BT
Stage IIA
IC HDR-BT boost 1.00
EBRT boost 1.81 (1.23- 2.91)
(1) IMRT boost 1.75 (1.04- 2.95)
(1) VMAT boost 1.97 (1.01- 3.84)
(2) Boost dose <20 1.64 (0.83- 3.22)
(2) Boost dose 1.98 (1.06- 3.70)
0.1 1.0 2.0 10.0
<- Overall Survival favor BT
Stage IIB
IC HDR-BT boost 1.00
EBRT boost 1.80 (1.37- 2.38)
(1) IMRT boost 1.88 (1.39- 2.56)
(1) VMAT boost 1.66 (1.13- 2.43)
(2) Boost dose <20 2.03 (1.37- 3.01)
(2) Boost dose 1.63 (1.13- 2.35)
0.1 1.0 2.0 10.0
<- Overall Survival favor BT
Stage III
IC HDR-BT boost 1.00
EBRT boost 1.44 (1.14- 1.81)
(1) IMRT boost 1.43 (1.11- 1.85)
(1) VMAT boost 1.44 (1.04- 2.01)
(2) Boost dose <20 1.34 (0.93- 1.94)
(2) Boost dose 1.49 (1.13- 1.96)
0.1 1.0 2.0 10.0
<- Overall Survival favor BT



Supplementary Figure 1. Adjusted hazard ratios of all-cause mortality for propensity score-matched cohorts receiving treatment with different contemporary EBRT techniques and boost dosages. EBRT, external beam radiotherapy; IC, intracavitary; CI, confidence interval; HR, hazard ratio. *All variables in **Table 2** were used in the multivariae analysis.



Supplementary Figure 2. The timeline of EBRT boost or IC HDR-BT boost. EBRT, external beam radiotherapy; HDR, high dose rate; BT, brachytherapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy.