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Original Article

Brachytherapy utilization rate and effect on survival in cervical cancer patients in Korea

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Synopsis
This study examined the brachytherapy utilization rate and evaluated the effect

ABSTRACT

Objective: External beam radiation therapy (EBRT) with concurrent chemotherapy followed by intracavitary brachytherapy is the standard treatment in locally advanced cervical cancer. This study examined the brachytherapy utilization rate and evaluated the effect of brachytherapy on survival in cervical cancer patients in Korea.
Methods: In this study, data from the Korea Central Cancer Registry and Korean National Health Insurance Service and data on mortality from Statistics Korea were linked and used. Patients with other cancers, distant metastasis at diagnosis, or unknown stage or who underwent hysterectomy were excluded. A total of 12,721 cervical cancer patients were analyzed in this study.
Results: The brachytherapy utilization rate (%) was calculated as the proportion of patients who received brachytherapy among those who received curative EBRT. The brachytherapy utilization rate decreased from 84% in 2005 to 78% in 2013 (p<0.001). Brachytherapy utilization rates varied by region, ranging from 72% to 100% except for in Jeju Island, where the rate was 56%. The brachytherapy utilization rate was lower in patients older than 80 years; patients with localized disease, non-squamous cell carcinoma, or Charlson comorbidity index 3 or more; patients diagnosed after 2010; patients from certain regions; patients receiving medical aid; and patients who underwent gynecologic procedures. Multivariable Cox regression analysis showed that brachytherapy when added to curative EBRT was independently associated with better cancer-specific survival (CSS) and overall survival (OS) than curative EBRT only.
Conclusion: The brachytherapy utilization rate decreased from 2005 to 2013 and varied by region in Korea. Brachytherapy use is independently associated with significantly higher CSS and OS in cervical cancer.

Keywords: Uterine Cervical Neoplasms; Brachytherapy; Radiotherapy; Survival; Korea

INTRODUCTION

Cervical cancer was the seventh most common female cancer in Korea in 2017, although the incidence has decreased due to effective screening and human papillomavirus vaccination [1]. Early-stage cervical cancer patients can be cured by surgical procedures. However, for

of brachytherapy on survival in cervical cancer patients in Korea. We used data from the Korea Central Cancer Registry and Korean National Health Insurance Service. Brachytherapy use is independently associated with significantly higher survival.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: K.Y.J.; Data curation: Y.M.S., P.M., C.M.G., K.S.Y.; Formal analysis: Y.M.S., P.M.; Methodology: K.Y.J.; Project administration: K.Y.A., K.Y.J.; Supervision: K.Y.A., K.Y.J.; Visualization: K.Y.A.; Writing - original draft: K.Y.A., K.Y.J.; Writing - review & editing: K.Y.J.

locally advanced cervical cancer patients, curative external beam radiation therapy (EBRT) with concurrent chemotherapy followed by intracavitary brachytherapy is the standard treatment [2,3].

Brachytherapy is a resource-intensive and technically challenging procedure compared to EBRT [4]. Safe storage and regular replacement of the radioisotope are additional difficulties when maintaining a brachytherapy center. From 1997 to 2014, the number of brachytherapy units decreased while the total number of radiotherapy facilities doubled in Korea. Only one-third (28 out of 86) of radiation oncology centers performed brachytherapy in patients in 2014 [5].

In the U.S., the brachytherapy utilization rate decreased from 83% in 1988 to 58% in 2009, which had a detrimental effect on survival in cervical cancer patients [6]. However, the brachytherapy utilization rate and its effect on survival had never been assessed in Korea. This study examined the brachytherapy utilization rate and evaluated the effect of brachytherapy on survival in cervical cancer patients in Korea.

MATERIALS AND METHODS

In this study, data from the Korea Central Cancer Registry (KCCR) and Korean National Health Insurance Service (KNHIS) and data on mortality from Statistics Korea were linked and used. The KCCR is a population-based cancer registry and includes more than 98% of cancer patients diagnosed in Korea [7,8]. KNHIS claims data consists of data from claims made by medical institutions collected by the National Health Insurance Corporation, Korea's single-payer insurer, and includes data on insurance eligibility, medical history, and prescription details [9]. This study was approved by the Institutional Review Board (IRB) of the National Cancer Center and Cancer Research Institute in Korea (IRB No. NCC2015-0217).

1. Study population

Data from patients diagnosed with cervical cancer (International Classification of Diseases, 10th revision [ICD-10] code C53) [10] between 2005 and 2013 were reviewed for the study. Those with other cancers were excluded from this study. Moreover, patients with distant metastasis or unknown Surveillance, Epidemiology, and End Results (SEER) summary stage, patients who did not use any medical services for their cervical cancer according to KCCR data linked with KNHIS, and patients who underwent hysterectomy were excluded. Among patients who received both EBRT and brachytherapy, ten patients received brachytherapy first. The median time interval between brachytherapy and EBRT in these patients was 708 days (range, 244–2,060 days). These ten patients were excluded due to the long interval between brachytherapy and EBRT. A total of 12,721 patients were analyzed in this study (**Fig. 1**).

2. Statistical analysis

We collected the following data: age at diagnosis, stage, histology, year of diagnosis, region, socioeconomic status, comorbidities, and gynecologic procedures. Socioeconomic status was defined by income, taken from the insurance claim at diagnosis (receiving medical aid, 0–25 percentile, 26–50 percentile, 51–75 percentile, 76–100 percentile, unknown). Charlson Comorbidity Index (CCI) scores were calculated one year before and one year after the cancer diagnosis and categorized as 0, 1, 2, or 3+. For the purpose of determining comorbidities, patients were defined as having hypertension (I10–I13), diabetes (E10–E14), hepatitis (B15–B19), tuberculosis (A15–A19), or hyperlipidemia (E78) if they received medical services

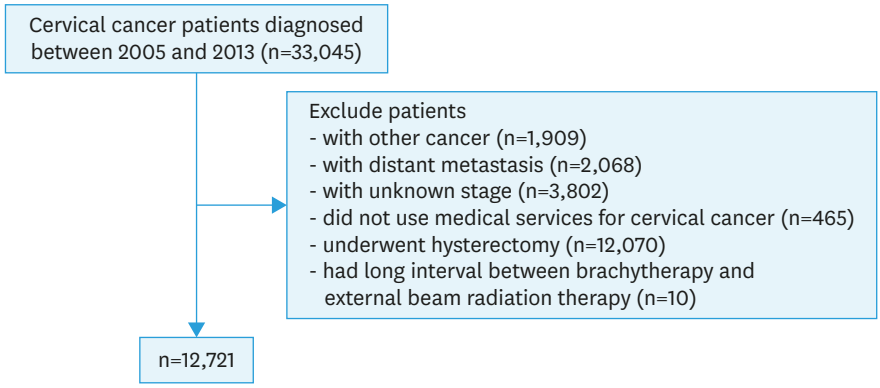

Fig. 1. Flow chart of patient selection.

for the respective disease at least once since 2005. Gynecologic procedures included loop electrosurgical excision procedure (LEEP), conization, and trachelectomy. The death-related variables were confirmed using data from the National Statistical Office, and the study end date was December 31, 2014.

To test for an association between year and brachytherapy utilization rate, the Cochrane-Armitage test was used. Multivariable regression analysis was performed to identify the factors that influenced the brachytherapy utilization rate. Cox proportional hazards regression was performed for cancer-specific survival (CSS) and overall survival (OS) to determine the factors affecting survival in patients with cervical cancer. The survival rate was estimated by the Kaplan-Meier method, and significance was reviewed via the log-rank test. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and a p-value <0.05 was considered statistically significant.

RESULTS

1. Patient and tumor characteristics

The median follow-up time was 50 months (range, 0–120 months). The patient and tumor characteristics are summarized in **Table 1**. The median age was 53 years old (range, 6–97 years old). The youngest patient, who was six years old at diagnosis, had clear cell adenocarcinoma and was treated with a gynecologic procedure only. The disease was localized in 65.6% of the patients. The major histology was squamous cell carcinoma (85.9%). EBRT with 20 or more fractions was defined as 'curative EBRT' and EBRT with less than 20 fractions as 'palliative EBRT.' The study subjects were classified into 7 groups: Group 1 - curative EBRT only (n=1,210); Group 2 - palliative EBRT and brachytherapy (n=370); Group 3 - brachytherapy only (n=238); Group 4 - curative EBRT and brachytherapy (n=4,707); Group 5 - palliative EBRT only (n=348); Group 6 - gynecologic procedure without RT (n=4,057); Group 7 - no treatment (n=1,791). In Group 6, 96.8% of patients had localized disease.

2. Brachytherapy utilization rate

The brachytherapy utilization rate (%) was calculated as the proportion of patients who received brachytherapy among those who received curative EBRT (number of patients in Group 4×100/ number of patients in Group 1 and Group 4). The brachytherapy utilization rate decreased from 84% in 2005 to 78% in 2013 (p<0.001 by Cochrane-Armitage test).

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Table 1. Patient and tumor characteristics

Characteristics	Total (n=12,721)	Group 1 (n=1,210)	Group 2 (n=370)	Group 3 (n=238)	Group 4 (n=4,707)	Group 5 (n=348)	Group 6 (n=4,057)	Group 7 (n=1,791)
Age (median: 53 yr)								
<Median age	6,243 (49.1)	447 (36.9)	120 (32.4)	84 (35.3)	1,666 (35.4)	96 (27.6)	3,133 (77.2)	697 (38.9)
≥Median age	6,478 (50.9)	763 (63.1)	250 (67.6)	154 (64.7)	3,041 (64.6)	252 (72.4)	924 (22.8)	1,094 (61.1)
Stage								
Localized	8,351 (65.6)	710 (58.7)	135 (36.5)	93 (39.1)	1,975 (42.0)	171 (49.1)	3,928 (96.8)	1,339 (74.8)
Regional metastasis	4,370 (34.4)	500 (41.3)	235 (63.5)	145 (60.9)	2,732 (58.0)	177 (50.9)	129 (3.2)	452 (25.2)
Histology								
Squamous cell carcinoma	10,927 (85.9)	986 (81.5)	325 (87.8)	208 (87.4)	4,088 (86.8)	299 (85.9)	3,626 (89.4)	1,395 (77.9)
Non-squamous cell carcinoma	1,794 (14.1)	224 (18.5)	45 (12.2)	30 (12.6)	619 (13.2)	49 (14.1)	431 (10.6)	396 (22.1)
Year of diagnosis								
2005	1,246 (9.8)	91 (7.5)	23 (6.2)	19 (8.0)	479 (10.2)	52 (14.9)	334 (8.2)	248 (13.8)
2006	1,367 (10.7)	128 (10.6)	19 (5.1)	23 (9.7)	565 (12.0)	23 (6.6)	429 (10.6)	180 (10.1)
2007	1,271 (10.0)	135 (11.2)	29 (7.8)	29 (12.2)	492 (10.5)	30 (8.6)	386 (9.5)	170 (9.5)
2008	1,442 (11.3)	129 (10.7)	28 (7.6)	43 (18.1)	551 (11.7)	41 (11.8)	448 (11.0)	202 (11.3)
2009	1,475 (11.6)	124 (10.2)	65 (17.6)	35 (14.7)	546 (11.6)	48 (13.8)	462 (11.4)	195 (10.9)
2010	1,583 (12.4)	145 (12.0)	114 (30.8)	31 (13.0)	484 (10.3)	49 (14.1)	546 (13.5)	214 (11.9)
2011	1,459 (11.5)	135 (11.2)	74 (20.0)	26 (10.9)	480 (10.2)	34 (9.8)	514 (12.7)	196 (10.9)
2012	1,432 (11.3)	167 (13.8)	8 (2.2)	15 (6.3)	558 (11.9)	33 (9.5)	449 (11.1)	202 (11.3)
2013	1,446 (11.4)	156 (12.9)	10 (2.7)	17 (7.1)	552 (11.7)	38 (10.9)	489 (12.1)	184 (10.3)
Region								
Seoul	2,415 (19.0)	239 (19.8)	78 (21.1)	68 (28.6)	739 (15.7)	97 (27.9)	902 (22.2)	292 (16.3)
Busan	994 (7.8)	111 (9.2)	3 (0.8)	13 (5.5)	279 (5.9)	23 (6.6)	365 (9.0)	200 (11.2)
Daegu	830 (6.5)	44 (3.6)	4 (1.1)	8 (3.4)	395 (8.4)	16 (4.6)	247 (6.1)	116 (6.5)
Incheon	686 (5.4)	71 (5.9)	11 (3.0)	3 (1.3)	274 (5.8)	17 (4.9)	201 (5.0)	109 (6.1)
Gyeonggi	2,601 (20.4)	252 (20.8)	64 (17.3)	58 (24.4)	930 (19.8)	71 (20.4)	882 (21.7)	344 (19.2)
Gamgwon	483 (3.8)	37 (3.1)	14 (3.8)	8 (3.4)	222 (4.7)	9 (2.6)	129 (3.2)	64 (3.6)
Chungbuk	390 (3.1)	30 (2.5)	20 (5.4)	5 (2.1)	179 (3.8)	8 (2.3)	97 (2.4)	51 (2.8)
Chungnam	605 (4.8)	84 (6.9)	13 (3.5)	8 (3.4)	249 (5.3)	17 (4.9)	157 (3.9)	77 (4.3)
Jeonbuk	380 (3.0)	32 (2.6)	10 (2.7)	9 (3.8)	170 (3.6)	10 (2.9)	91 (2.2)	58 (3.2)
Jeonnam	561 (4.4)	43 (3.6)	61 (16.5)	12 (5.0)	227 (4.8)	15 (4.3)	118 (2.9)	85 (4.7)
Gyeongbuk	739 (5.8)	82 (6.8)	12 (3.2)	8 (3.4)	351 (7.5)	22 (6.3)	171 (4.2)	93 (5.2)
Gyeongnam	777 (6.1)	74 (6.1)	10 (2.7)	25 (10.5)	259 (5.5)	14 (4.0)	256 (6.3)	139 (7.8)
Jeju	125 (1.0)	27 (2.2)	- (0.0)	1 (0.4)	34 (0.7)	1 (0.3)	34 (0.8)	28 (1.6)
Gwangju	441 (3.5)	16 (1.3)	53 (14.3)	6 (2.5)	171 (3.6)	7 (2.0)	134 (3.3)	54 (3.0)
Daejeon	535 (4.2)	56 (4.6)	6 (1.6)	4 (1.7)	191 (4.1)	11 (3.2)	206 (5.1)	61 (3.4)
Ulsan	146 (1.1)	12 (1.0)	11 (3.0)	2 (0.8)	31 (0.7)	10 (2.9)	63 (1.6)	17 (0.9)
Sejong	10 (0.1)	- (0.0)	- (0.0)	- (0.0)	5 (0.1)	- (0.0)	4 (0.1)	1 (0.1)
Traveler	2 (0.0)	- (0.0)	- (0.0)	- (0.0)	1 (0.0)	- (0.0)	- (0.0)	1 (0.1)
Unknown	1 (0.0)	- (0.0)	- (0.0)	- (0.0)	- (0.0)	- (0.0)	- (0.0)	1 (0.1)
Socioeconomic status								
Receiving medical aid	1,474 (11.6)	181 (15.0)	43 (11.6)	21 (8.8)	537 (11.4)	76 (21.8)	274 (6.8)	342 (19.1)
0–25 percentile	2,790 (21.9)	282 (23.3)	71 (19.2)	40 (16.8)	1,123 (23.9)	73 (21.0)	814 (20.1)	387 (21.6)
26–50 percentile	2,748 (21.6)	227 (18.8)	88 (23.8)	41 (17.2)	1,033 (21.9)	67 (19.3)	975 (24.0)	317 (17.7)
51–75 percentile	2,666 (21.0)	224 (18.5)	85 (23.0)	52 (21.8)	959 (20.4)	59 (17.0)	965 (23.8)	322 (18.0)
76–100 percentile	3,037 (23.9)	296 (24.5)	83 (22.4)	84 (35.3)	1,053 (22.4)	71 (20.4)	1,029 (25.4)	421 (23.5)
Unknown	6 (0.0)	- (0.0)	- (0.0)	- (0.0)	2 (0.0)	2 (0.6)	- (0.0)	2 (0.1)
Charlson comorbidity index (1 yr after cancer diagnosis)								
0	4,635 (36.4)	335 (27.7)	93 (25.1)	100 (42.0)	1,439 (30.6)	84 (24.1)	1,900 (46.8)	684 (38.2)
1	3,587 (28.2)	334 (27.6)	127 (34.3)	63 (26.5)	1,285 (27.3)	81 (23.3)	1,246 (30.7)	451 (25.2)
2	2,082 (16.4)	220 (18.2)	62 (16.8)	41 (17.2)	858 (18.2)	67 (19.3)	530 (13.1)	304 (17.0)
3+	2,417 (19.0)	321 (26.5)	88 (23.8)	34 (14.3)	1,125 (23.9)	116 (33.3)	381 (9.4)	352 (19.7)
Charlson comorbidity index (1 yr before cancer diagnosis)								
0	5,997 (47.1)	473 (39.1)	158 (42.7)	98 (41.2)	2,073 (44.0)	113 (32.5)	2,270 (56.0)	812 (45.3)
1	3,318 (26.1)	327 (27.0)	88 (23.8)	64 (26.9)	1,236 (26.3)	83 (23.9)	1,118 (27.6)	402 (22.4)
2	1,532 (12.0)	165 (13.6)	53 (14.3)	33 (13.9)	649 (13.8)	50 (14.4)	367 (9.0)	215 (12.0)
3+	1,874 (14.7)	245 (20.2)	71 (19.2)	43 (18.1)	749 (15.9)	102 (29.3)	302 (7.4)	362 (20.2)
Gynecologic procedures								
No	6,883 (54.1)	844 (69.8)	262 (70.8)	181 (76.1)	3,531 (75.0)	274 (78.7)	- (0.0)	1,791 (100.0)
Yes	5,838 (45.9)	366 (30.2)	108 (29.2)	57 (23.9)	1,176 (25.0)	74 (21.3)	4,057 (100.0)	- (0.0)

Values are presented as number (%).

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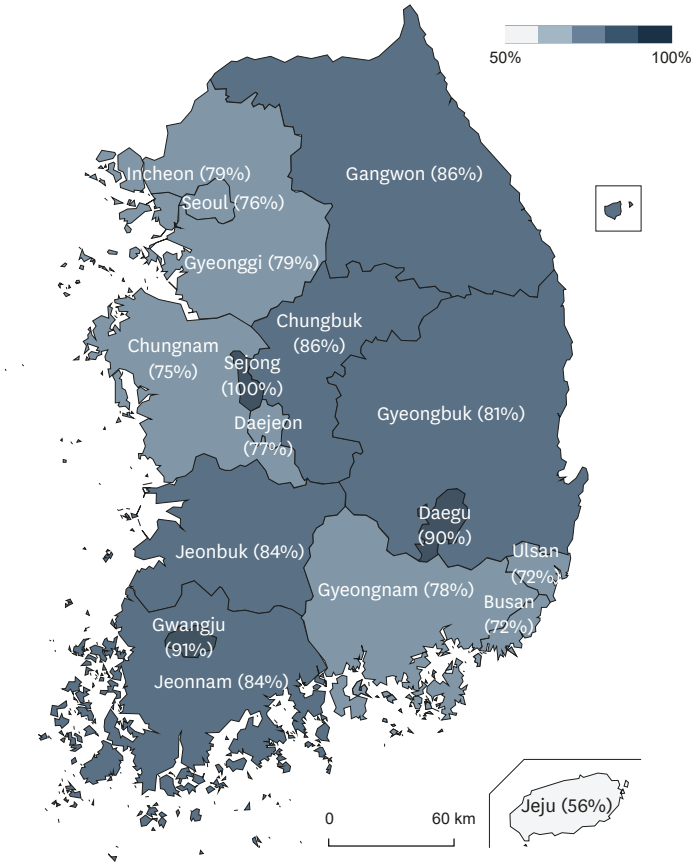

Fig. 2. Brachytherapy utilization rates by region.

Brachytherapy utilization rates by region are displayed in **Fig. 2**. The rates vary by region, ranging from 72% to 100% except for in Jeju Island, where the rate was 56%.

3. Predictors of brachytherapy utilization

The brachytherapy utilization rate was lower in patients older than 80 years; patients with localized disease, non-squamous cell carcinoma, or Charlson comorbidity index 3 or more; patients diagnosed after 2010; patients from certain regions; patients receiving medical aid; and patients who underwent gynecologic procedures (**Table 2**).

4. Survival

CSS rates in all seven groups are shown in **Fig. 3A**. Group 6 (gynecologic procedure without RT) had the best survival rate, and Group 5 (palliative EBRT only) the worst. Among patients who received curative EBRT, Group 4 (curative EBRT and brachytherapy) achieved a higher 5-year CSS than Group 1 (curative EBRT only), 76.3% vs. 67.0% ($p<0.001$) (**Fig. 3B**). OS rates in all seven groups are shown in **Fig. S1A**. Group 4 achieved a higher 5-year OS than Group 1, 73.1% vs. 62.6% ($p<0.001$) (**Fig. S1B**).

Multivariable Cox regression analysis showed that brachytherapy when added to curative EBRT was independently associated with better CSS (hazard ratio [HR]=0.58; 95% confidence interval [CI]=0.52–0.66; $p<0.001$) and OS (HR=0.59; 95% confidence interval

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Table 2. Predictors of brachytherapy utilization

Characteristics	Brachytherapy utilization rate (%)	Univariable			Multivariable*		
		OR	95% CI	p-value	OR	95% CI	p-value
Age							
<50 yr	78.0	Ref			Ref		
50–79 yr	81.4	1.24	1.08–1.43	0.003	1.36	1.17–1.59	<0.001
≥80 yr	66.9	0.57	0.45–0.73	<0.001	0.66	0.51–0.87	0.003
Stage							
Localized	73.6	Ref			Ref		
Regional metastasis	84.5	1.96	1.73–2.23	<0.001	1.98	1.73–2.26	<0.001
Histology							
Squamous cell carcinoma	80.6	Ref			Ref		
Non-squamous cell carcinoma	73.4	0.67	0.56–0.79	<0.001	0.68	0.57–0.81	<0.001
Year of diagnosis							
2005	84.0	Ref			Ref		
2006	81.5	0.84	0.62–1.13	0.243	0.86	0.64–1.16	0.328
2007	78.5	0.69	0.52–0.93	0.014	0.69	0.51–0.93	0.015
2008	81.0	0.81	0.60–1.09	0.166	0.76	0.56–1.03	0.079
2009	81.5	0.84	0.62–1.13	0.240	0.88	0.65–1.20	0.425
2010	76.9	0.63	0.47–0.85	0.002	0.67	0.49–0.90	0.008
2011	78.0	0.68	0.50–0.91	0.009	0.67	0.49–0.91	0.009
2012	77.0	0.64	0.48–0.84	0.002	0.65	0.49–0.87	0.004
2013	78.0	0.67	0.51–0.90	0.007	0.65	0.48–0.87	0.004
Region†							
Seoul	75.6	Ref			Ref		
Busan	71.5	0.81	0.62–1.06	0.124	0.85	0.65–1.12	0.239
Daegu	90.0	2.90	2.06–4.10	<0.001	3.15	2.22–4.47	<0.001
Incheon	79.4	1.25	0.93–1.68	0.146	1.24	0.91–1.68	0.178
Gyeonggi	78.7	1.19	0.98–1.46	0.085	1.22	0.99–1.50	0.057
Gamgwon	85.7	1.94	1.33–2.83	0.001	1.90	1.29–2.79	0.001
Chungbuk	85.6	1.93	1.28–2.92	0.002	1.83	1.21–2.79	0.005
Chungnam	74.8	0.96	0.72–1.28	0.773	0.96	0.72–1.29	0.781
Jeonbuk	84.2	1.72	1.15–2.58	0.009	1.70	1.13–2.56	0.012
Jeonnam	84.1	1.71	1.20–2.44	0.003	1.64	1.14–2.36	0.008
Gyeongbuk	81.1	1.38	1.05–1.83	0.023	1.43	1.07–1.90	0.016
Gyeongnam	77.8	1.13	0.84–1.52	0.413	1.09	0.80–1.47	0.585
Jeju	55.7	0.41	0.24–0.69	0.001	0.36	0.21–0.63	<0.001
Gwangju	91.4	3.46	2.03–5.89	<0.001	3.35	1.95–5.75	<0.001
Daejeon	77.3	1.10	0.79–1.54	0.562	1.08	0.77–1.52	0.649
Socioeconomic status							
Receiving medical aid	74.8	Ref			Ref		
0–50 percentile	80.9	1.43	1.18–1.73	<0.001	1.46	1.19–1.80	<0.001
51–100 percentile	79.5	1.30	1.07–1.58	0.007	1.37	1.12–1.68	0.003
Charlson comorbidity index (1 yr before cancer diagnosis)							
0	81.4	Ref			Ref		
1–2	79.3	0.87	0.76–1.01	0.061	0.89	0.77–1.04	0.143
3+	75.4	0.70	0.59–0.83	<0.001	0.75	0.62–0.91	0.004
Gynecologic procedures							
No	80.7	Ref			Ref		
Yes	76.3	0.77	0.67–0.88	0.0002	0.85	0.73–0.98	0.026

CI, confidence interval; OR, odds ratio.
*Stepwise selection with p-value entry criteria of 0.1; †Ulsan and Sejong were excluded because of the small number of patients.

[CI]=0.53–0.67; p<0.001) than curative EBRT only (**Table 3** and **Table S1**). Younger age, earlier stage, squamous histology, year of diagnosis after 2011, higher socioeconomic status and lower Charlson comorbidity index (1 year after the cancer diagnosis) were also independently associated with better CSS and OS.

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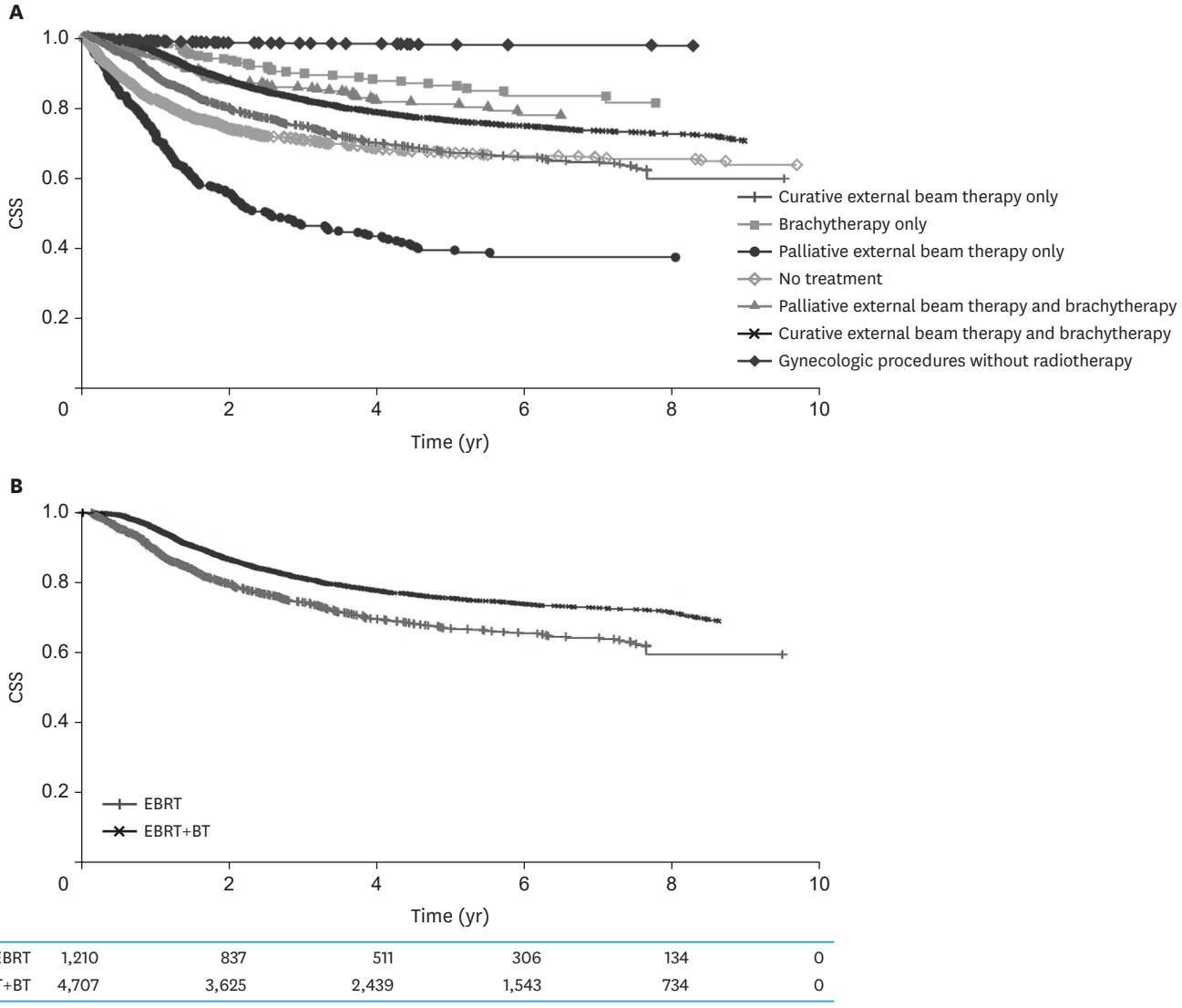

EBRT	1,210	837	511	306	134	0
EBRT+BT	4,707	3,625	2,439	1,543	734	0

Fig. 3. (A) CSS rates in all seven groups (B) CSS rates in Group 1 and Group 4.
BT, brachytherapy; CSS, cancer-specific survival; EBRT, external beam radiation therapy.

DISCUSSION

The present study is the first to investigate brachytherapy's effect on survival in cervical cancer patients in Korea. We found that brachytherapy use is independently associated with significantly higher CSS and OS. This finding is consistent with a study from the United States based on 18 SEER population-based registries [6]. This study's strength is that our database includes the entire Korean population, whereas the 18 SEER population-based registries covered only 28% of the U.S. population.

We also found that the brachytherapy utilization rate has decreased. These findings were in line with the results of a national survey in 2015 [5]. According to this survey, the percentage of brachytherapy facilities among radiation oncology centers has decreased 28.2% between 2006 (65.0%, 39 of 60) and 2014 (36.8%, 28 of 76). The survey found the main reasons

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Table 3. Cancer-specific survival

Characteristics	No.	Univariable			Multivariable*		
		HR	95% CI	p-value	HR	95% CI	p-value
Age (median: 53 yr)							
<Median age	6,243	Ref			Ref		
≥Median age	6,478	2.74	2.50–3.00	<0.001	1.53	1.39–1.68	<0.001
Stage							
Localized	8,351	Ref			Ref		
Regional metastasis	4,370	3.13	2.88–3.39	<0.001	2.21	2.02–2.42	<0.001
Histology							
Squamous cell carcinoma	10,927	Ref			Ref		
Non-squamous cell carcinoma	1,794	1.64	1.48–1.82	<0.001	1.49	1.34–1.65	<0.001
Year of diagnosis							
2005–2006	2,613	Ref			Ref		
2007–2008	2,713	0.97	0.87–1.08	0.579	0.98	0.88–1.10	0.787
2009–2010	3,058	0.88	0.78–0.98	0.025	0.92	0.82–1.03	0.157
2011–2012	2,891	0.81	0.71–0.92	0.001	0.84	0.74–0.96	0.010
2013	1,446	0.83	0.69–1.01	0.066	0.79	0.64–0.96	0.018
Region†							
Seoul	2,415	Ref					
Busan	994	1.13	0.95–1.34	0.161			
Daegu	830	0.88	0.72–1.07	0.193			
Incheon	686	1.25	1.03–1.51	0.021			
Gyeonggi	2,601	1.06	0.93–1.21	0.407			
Gamgwon	483	1.20	0.97–1.50	0.101			
Chungbuk	390	1.13	0.88–1.45	0.339			
Chungnam	605	1.24	1.01–1.51	0.036			
Jeonbuk	380	1.16	0.91–1.49	0.227			
Jeonnam	561	1.35	1.11–1.65	0.003			
Gyeongbuk	739	1.21	1.00–1.46	0.046			
Gyeongnam	777	1.27	1.06–1.52	0.009			
Gwangju	441	1.00	0.79–1.28	0.986			
Daejeon	535	0.68	0.52–0.88	0.003			
Socioeconomic status (unknown n=6)							
Receiving medical aid	1,474	Ref			Ref		
0–50 percentile	5,538	0.66	0.59–0.74	<0.001	0.97	0.86–1.09	0.604
51–100 percentile	5,703	0.58	0.52–0.65	<0.001	0.86	0.76–0.97	0.013
Charlson comorbidity index (1 yr after cancer diagnosis)							
0	4,635	Ref			Ref		
1–2	5,669	1.61	1.45–1.77	<0.001	1.40	1.26–1.55	<0.001
3+	2,417	2.83	2.54–3.15	<0.001	1.82	1.62–2.04	<0.001
Treatment group							
Group 1. Curative external beam therapy only	1,210	Ref			Ref		
Group 2. Palliative external beam therapy and brachytherapy	370	0.53	0.41–0.69	<0.001	0.45	0.34–0.58	<0.001
Group 3. Brachytherapy only	238	0.38	0.26–0.54	<0.001	0.35	0.25–0.50	<0.001
Group 4. Curative external beam therapy and brachytherapy	4,707	0.66	0.59–0.75	<0.001	0.58	0.52–0.66	<0.001
Group 5. Palliative external beam therapy only	348	2.43	2.04–2.88	<0.001	2.14	1.79–2.55	<0.001
Group 6. Gynecologic procedures without radiotherapy	4,057	0.05	0.04–0.07	<0.001	0.10	0.08–0.13	<0.001
Group 7. No treatment	1,791	1.08	0.95–1.23	0.265	1.36	1.19–1.56	<0.001

CI, confidence interval; HR, hazard ratio.
*Stepwise selection with p-value entry criteria of 0.1; †Ulsan, Sejong and Jeju were excluded because of the small number of patients.

facilities were choosing not to perform brachytherapy were low medical reimbursement and the high cost of source replacement. Among facilities which perform brachytherapy, 75% still use 2D brachytherapy, which uses only orthogonal anterior-posterior and lateral X-ray images. With 2D brachytherapy, a dose is prescribed at point A, located 2 cm lateral and 2 cm cranial to the cervical os. Therefore, patients with a large uterus receive an underdose and those with a small uterus, receive an overdose.

Furthermore, the uterine perforation rate is around 8% during brachytherapy simulation [11]. Without a CT scan, it is impossible to know if perforation has occurred or not. Compared to CT, cervical cancers are more clearly shown on magnetic resonance imaging (MRI). It is well known that MRI-guided brachytherapy improves local control and decreases toxicity [12]. The improvement in local control may impact CSS. Indeed, the 5-year CSS was 89% in patients treated with MRI-guided brachytherapy at our center between 2008 and 2013 [13], which is much higher than the national average. However, in Korea, only 2 out of 28 brachytherapy centers are able to perform MRI-guided brachytherapy in 2020. MRI-guided brachytherapy is a time-intensive procedure for physicians and medical physicists and has high cost compared to 2D brachytherapy, but there is no additional medical reimbursement for MRI-guided brachytherapy. Therefore, MRI-guided brachytherapy is a burden to the hospital, and is sometimes discouraged. Additional reimbursement should be provided to encourage MRI-guided brachytherapy.

We observed significant geographic disparities in brachytherapy utilization in the present study. However, brachytherapy utilization rates are not correlated with the number of brachytherapy centers. For example, Chungbuk has no brachytherapy centers, but their brachytherapy utilization rate was 86%. This phenomenon might be due to the well-developed transport system in Korea. More than half of the brachytherapy centers are in the capital, Seoul, and its surrounding metropolitan areas according to the previously mentioned national survey [5]. Patients outside the metropolitan area can travel to receive brachytherapy. As suggested in the previous study, a well-organized referral system, and proper medical reimbursement for brachytherapy can increase the brachytherapy utilization rate in peninsular South Korea [5]. However, the brachytherapy utilization rate in Jeju Island was much lower than the peninsular average due to the geographic isolation. Hence, a brachytherapy center needs to be emplaced in Jeju Island to address this disparity.

In a recent study in the U.S., black women with locally advanced cervical cancer were less likely to receive brachytherapy, which mediated a survival difference by race [14]. In the present study, we observed that the brachytherapy utilization rate was lower in the patients receiving medical aid (74.8%) than those not receiving medical aid (median 80.0%, range 79.5%–80.9%, p=0.001). Improving access to brachytherapy in the medical aids group is needed to reduce survival disparities between socioeconomic groups.

Intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) were suggested as brachytherapy alternatives. However, IMRT and SBRT boost result in inferior OS as compared with brachytherapy [15]. In Korea, a multicenter retrospective study (KROG 1419) collected data from 11 hospitals from 2005 through 2012 [16]. A total of 75 patients were treated with EBRT, 3D-conformal radiotherapy in 24 patients and IMRT in 51 patients, in place of brachytherapy because of complicated anatomy (49%) or medical illness (20%). The 5-year local tumor control rate in those patients was 70.0%, which is inferior to that of MRI-guided brachytherapy (94%) [13]. The Korean national insurance system did not cover IMRT or SBRT boost at time of that study, so there was no data for those patients in the KCCR or KNHIS databases. Hence, we were not able to compare IMRT, or SBRT boost with brachytherapy in the present study, and this is one of the limitations of our study.

There were several other limitations in our study. Since the data was used for administrative claims purposes, clinical information such as tumor size and concurrent chemotherapy were not available. Because the aim of the EBRT (curative vs. palliative) was not available either, we applied

an arbitrary cut-off (20 fractions). Imbalances in patient and tumor characteristics between the brachytherapy group, and no brachytherapy group may have affected the clinical outcomes.

In the U.S., brachytherapy utilization declined during 2008–2010 compared to 2004–2007, and declines were larger for patients with government insurance than privately-insured patients. However, with the implementation of new policy in concert with researcher awareness, the brachytherapy utilization rate recovered during 2011–2014 in all insurance groups and was especially improved for Medicaid and uninsured patients [17]. Unlike the U.S., all patients are covered by government insurance in Korea. Therefore, we can effectively reverse the declining trend in brachytherapy utilization with a fair policy that encourages brachytherapy.

Brachytherapy use is independently associated with significantly higher CSS and OS in cervical cancer. Inadequacies in reimbursement should be resolved to prevent the further decrease of the brachytherapy utilization rate.

SUPPLEMENTARY MATERIALS

Table S1
Overall survival

Click here to view

Fig. S1
(A) OS rates in all seven groups (B) OS rates in Group 1 and Group 4.

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