

# Comparative Survival Assessment of Two-Dimension (2D) versus Three-Dimension (3D) Brachytherapy Treatment in Locally Advanced Cervical Cancer: A Retrospective Case Control Study

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**Objective:** To assess the efficacy as seen as overall survival, local control, progression free survival (PFS) and toxicities, between two-dimension (2D) and three-dimension (3D) computed tomography (CT) guided brachytherapy (BT) without using interstitial needles among patients with cervical cancer.

**Materials and Methods:** A retrospective case control study was performed among patients with FIGO stage IB-IVA cervical cancer treated between March 1990 and August 2018. Concurrent chemoradiation using external beam radiotherapy followed by BT was the treatment method used in all patients. Patients were divided in two groups based on imaging type during BT to compare between 2D and 3D BT techniques. Clinical endpoints were overall survival, local control, progression free survival, acute toxicities, and late toxicities.

**Results:** One hundred two patients with cervical cancer were included, which 52 patients had been treated with 2D and 50 patients with 3D using CT scan BT without interstitial needles. Baseline characteristics were similar between the groups. External beam was used among all patients during the concurrent chemoradiation period before BT. All patients completed the treatment. Similar 3-year overall survival and local control were reported between 2D and 3D techniques. Overall, the 3-year survival rate was 95.7% in 2D and 91.8% in 3D BT ( $p=0.188$ ). Local control at the 3-year follow-up was 88.6% for 2D and 93.3% for 3D treatment ( $p=0.571$ ). Progression free survival was better in the 2-D rather than the 3D group with 86.13% in 2D versus 27.4% in the 3D group ( $p=0.006$ ). No grade 3 or 4 toxicity regarding the 3D technique was observed whereas 1.9% of grade 3 presented acute gastrointestinal toxicity ( $p=1$ ), and grade 3 late gastrointestinal and genitourinary toxicities in the 2D technique group at 7.7 and 5.8%, respectively ( $p=1$ , both). The 3D BT significantly reduced acute grade 1 to 2 gastrointestinal side effect as 23% in the 2D versus 4% in 3D group ( $p=0.003$ ), and grade 1 to 2 late genitourinary side effect as 50% in the 2D versus 16% in the 3D group ( $p=0.001$ ).

**Conclusion:** Using CT guided 3D BT to treat cervical cancer showed similar outcomes in survival and local control but reduced toxicity compared with the 2D technique. Disease progression including metastasis was better in the 2D BT technique group. CT guided BT helped reduce dose to organs at risk and long-term follow-up for survival outcome and toxicities was needed.

**Keywords:** Cervical cancer; Brachytherapy technique; Brachytherapy; 3D brachytherapy; 2D brachytherapy

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Cervical cancer is one of the most common female cancers especially in low- and middle-income countries. Treatment modalities include surgery, radiation therapy, and systemic therapy depending on disease status such as staging and histopathology,

and patient status such as performance status and age. Concurrent chemoradiation followed by brachytherapy is considered to be standard treatment of locally advanced cervical cancer stage IB2-IVA in the FIGO staging 2008 or IB3, IIA2-IVA in the FIGO staging 2018<sup>(1-4)</sup>.

Boosting via brachytherapy was able to escalate a high dose to control the cervical mass without increasing pelvic toxicities. The brachytherapy technique has evolved over time from using plain film imaging (2D technique) to using computed tomography (CT) scan or magnetic resonance imaging (MRI) scan (3D technique).

In the 2D technique, the dose is prescribed to a virtual point A, fixed distance from the applicator. Pear-shaped isodose configuration was used in this conventional brachytherapy. Rectal and bladder

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point doses were measured related to the applicator location, so the nearby organ dose measurement might be inexact<sup>(5)</sup>.

In the 3D technique, using CT or MRI scan, cervical mass and nearby organs were obviously better observed than when using plain films. Dose prescription was given to high-risk clinical target volume (HR-CTV). Volume-based measurement was reported of the target dose and nearby normal organ, and interstitial needles may be added to brachytherapy applicators<sup>(6)</sup>.

Currently, in many centers, 3D techniques are used instead of 2D brachytherapy consuming much more resources. The present study aimed to evaluate the different outcomes between 2D and 3D brachytherapy without interstitial needles outcomes on overall survival (OS), progression free survival (PFS), local control (LC), and toxicities among patients with locally advanced, cervical cancer after being treated with concurrent chemoradiation.

## Materials and Methods

### Patient selection

The present study was a retrospective cohort study including patients with cervical cancer stage IB2-IVA in the FIGO staging 2008 or IB3, IIA2-IVA in the FIGO staging 2018. These patients were all treated with concurrent chemoradiation to the pelvis (+/- paraaortic lymph nodes) followed by brachytherapy (low dose rate [LDR] and high dose rate [HDR]) between March 1990 and August 2018. Every patient with cervical cancer had to complete radiation therapy and chemotherapy sessions. All patients were biopsy-proven to have cervical cancer, including squamous cell carcinoma, adenosquamous cell carcinoma, or adenocarcinoma. All patients were treated using conventional external beam radiation therapy (EBRT) technique.

### Study design

Patients were divided in two groups based on imaging type during brachytherapy to compare between 2D and 3D brachytherapy techniques. All patients were treated with concurrent chemoradiation therapy (CCRT) as the primary treatment. Brachytherapy treatment was performed using plain film in the 2D technique and CT scan in the 3D technique. The brachytherapy applicators were all without interstitial needles. Patient characteristics, cancer characteristics, cancer staging, treatments, outcomes, and complications of treatment were collected retrospectively. The present study was

approved by the Phramongkutklo Hospital Ethics Committee.

### Treatment characteristics

Locally advanced cervical cancer stage IB2-IV in the FIGO staging 2008 or IB3, IIA2-IVA in the FIGO staging 2018 was diagnosed based on physical examination and imaging data. Whole pelvic EBRT was used concurrent with chemotherapy. Four field techniques with 45 to 50 Gray in 25 fractions and 10 MV photons were prescribed. After external beam radiation, HDR brachytherapy was performed once weekly. Radioactive use in LDR brachytherapy was cesium-137 between 1990 and 2006, and HDR iridium-192 between 2007 and 2018. Almost all patients received platinum-based chemotherapy such as cisplatin and carboplatin. The minority received fluorouracil (FU) and mitomycin. Radiation and chemotherapy were all completed followed by standard treatments. All patients had to complete the total treatment time within eight weeks.

### External beam radiation therapy (whole pelvis)

Whole pelvic radiation therapy was used with four field conventional techniques, and 10 MV photon was prescribed. Radiation dose was from 45 to 50 Gy. Field design for pelvic radiation therapy was AP-PA and lateral fields.

AP-PA field borders were defined as:

- Superior at L4 to L5 vertebral interspace
  - Inferior at 2 cm below the obturator foramen or 3 cm inferior to distal disease, whichever was lower
  - Lateral at 1.5 to 2 cm lateral to the pelvic brim
- Lateral field borders were defined as:
- Superior the same as AP-PA field
  - Inferior the same as AP-PA field
  - Anterior at the anterior to pubic symphysis
  - Posterior at 0.5 cm posterior to the anterior border of the S2/3 vertebral junction, and may include the entire sacrum to cover the disease extent

### Concurrent chemotherapy details

Almost all patients received platinum-based chemotherapy such as 40 mg/m<sup>2</sup> of cisplatin weekly (n=92, 90%) or carboplatin AUC 2 weekly (n=7, 6.86%). The minority received 1,000 mg/m<sup>2</sup>/FU a day on days 1 to 4 and 29 to 32 and 10 mg/m<sup>2</sup> of mitomycin a day on day 1 and day 29 (n=3, 2.94%).

### Brachytherapy specifications

Brachytherapy using tandem and ovoid application without interstitial needles was used in

both 2D and 3D techniques.

In the 2D technique, plain film of the lower abdomen was used after applicator insertion. According to ICRU 38<sup>(5)</sup>, dose prescription was set 100% at point A. Dose fractionation such as 6.5 Gy  $\times$  4 times, 7.5 Gy  $\times$  3 times, and 8.3 Gy  $\times$  2 times, was prescribed. Normal organ dose constraint was described as bladder and rectal point from plain film.

In the 3D technique, a CT scan without contrast media was performed followed by applicator insertion. Pre-brachytherapy MRI scan was performed in every case since 2017 to evaluate the disease extension. According to GEC-ESTRO guidelines<sup>(4)</sup>, target volume, HR-CTV, and intermediate risk clinical target volume (IR-CTV) were used in dose prescription instead of point A. HR-CTV covered the gross tumor at the time of brachytherapy determined by both pre-brachytherapy MRI image and at the exam, the entire cervix and regions of indeterminate T2-weighted MRI signal and the gray zone. IR-CTV was determined for HR-CTV with an asymmetric expansion, not extending to organs at risks (OARs) and including sites of initial involvement.

Dose distribution depended on the standard loading system of tandem and ovoid. OAR such as rectal and bladder radiation dose was measured using D2cc (minimal dose to the most irradiated 2 cc of OAR). A target dose volume histogram was used for dose to 90% and 95% of the target volume. The total dose was calculated including external beam radiation dose and brachytherapy dose using tumor-equivalent dose (EQD210) and OAR-equivalent dose (EQD23). Dose fractionation such as 6.5 Gy  $\times$  4 times, 7.5 Gy  $\times$  3 times, and 8.3 Gy  $\times$  2 times were prescribed.

LDR brachytherapy delivers radiation at a dose of LDR brachytherapy at 0.55 to 0.65 Gy/hour. Point A doses were 75 Gy in two fractions for LDR. Patients who received intrauterine tandem and ovoid were hospitalized after placement of the applicator for 24 to 72 hours to allow radiation therapy treatment. Cs-137 LDR radioactive source was applied for intracavitary brachytherapy treatment and was determined using the Manchester System between 1990 and 2006.

HDR brachytherapy delivered a dose greater than 12 Gy/hour in the outpatient setting. Short duration of brachytherapy treatment time and patient convenience were the advantages over LDR brachytherapy. 192Ir HDR sources were used in HDR brachytherapy between 2007 and 2019.

At the present study institute, brachytherapy treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA) has been used. The optimization

process included equal times, geometric optimization (GO) and volume optimization (VO). In 3D brachytherapy, contouring of the target volume and normal organs at risk comprised the input. The GO was performed followed by isodose reshaping by manual adjustments of isodose lines. The isodose lines were adjusted to optimize between target volume dose and critical structure dose.

### Endpoints

The primary endpoint of this retrospective cohort was overall survival, defined as from the first date of treatment to death from any cause. The secondary endpoints were local control rate, defined as the time from treatment start to pelvic or vaginal recurrence of the disease evidenced from physical examination, imaging, and biopsy (if performed), PFS, defined as the time from treatment start until tumor progression (PD) from physical examination, imaging, or biopsy (if performed), acute toxicities, defined as toxicities during radiation therapy session to three months after radiation therapy, and late toxicities, defined as toxicities more than three months after radiation therapy. Acute and late toxicities were evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 5. Defining of toxicities are detailed below:

Grade 1: mild, asymptomatic, or mild symptoms, clinical or diagnostic observations only, intervention not indicated

Grade 2: moderate, minimal, local, or non-invasive intervention indicated, limiting age-appropriate instrumental ADL

Grade 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care ADL

Grade 4: life-threatening consequences, urgent intervention indicated

Grade 5: death related to adverse event

Minimal follow-up required at least three years.

### Statistical analysis

Patient and disease characteristics were described using percentage, mean, and standard deviation with differences using the chi-square test. Overall survival, local control, and PFS were all calculated from the treatment date to the date of events or lost to follow-up. Kaplan-Meier survival method and log rank test were used to calculate the time to event. Acute and late toxicities were measured using chi-square tests. A p-value of less than 0.05 was defined as statistically

significant. Analysis using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA) was performed.

## Results

### Patient and treatment characteristics

One hundred two patients with cervical cancer were retrospectively registered in the present study. All patients completed the standard treatment, which is concurrent chemoradiation and brachytherapy. The 2D technique was used on 52 patients and the 3D technique was used on the other 50 patients. All patients used HDR brachytherapy without interstitial needles insertion (Table 1). Patient characteristics including the FIGO staging, pathology, underlying disease, and age at diagnosis were described and compared between 2D and 3D techniques. All patient characteristics indicated no statistically significant difference between 2D and 3D technique ( $p < 0.05$ ) (Table 1).

### Outcomes

The follow-up time in the 2D technique ranged between six and 30 years and the 3D technique ranged between three and five years. Lost to follow-up was measured at 13.7% of all populations (14 of 102 patients).

### Overall survival

Ninety-six of 102 patients were alive at the time of analysis. The overall survival rate was 94.12% at 3-year follow-up. Two patients (1.96%) died from cervical cancer while four patients (3.9%) died from other conditions such as UTI septicemia or other underlying disease conditions.

Overall, the 3-year survival rate was 95.65% in 2D and 91.79% in 3D brachytherapy ( $p = 0.188$ ) without statistically significant difference (Figure 1).

### Local control

In all, 94 of 102 patients achieved the three-year local control. Local recurrence was observed among eight patients. Local control was 92.16% at the three-year mark. Between the 2D and the 3D techniques, no difference was observed of the three-year local control rate with 2D being 88.59% (74.53 to 95.13) and 3D being 93.33% (80.67 to 97.81) ( $p = 0.571$ ) (Figure 2).

### Progression free survival

Overall PFS was 85.29% (87 of 102 patients). The three-year PFS rate was 86.13% in 2D and

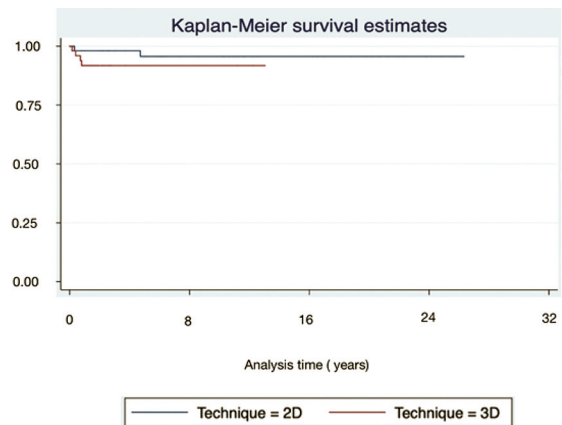


Figure 1. Overall survival.

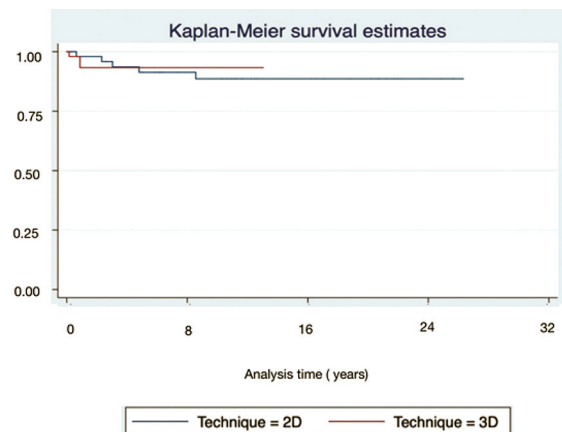


Figure 2. Local control.

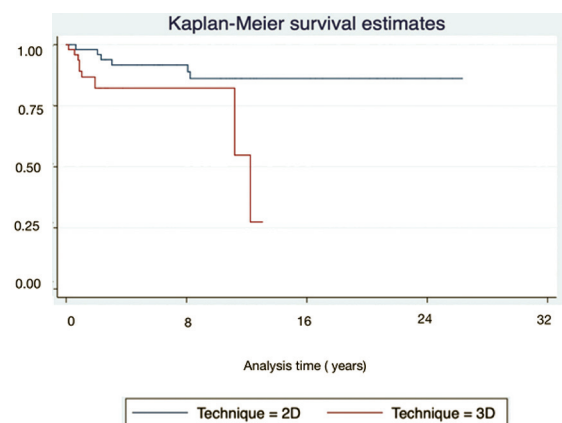


Figure 3. Progression free survival.

27.14% in 3D ( $p = 0.006$ ). In the present analysis, the 2D technique seemed to present better PFS than the 3D technique (Figure 3).

**Table 1.** Baseline characteristics

Baseline characteristics	Total (n=102); n (%)	Technique 2D (n=52); n (%)	Technique 3D (n=50); n (%)	p-value <sup>#</sup>
FIGO staging				0.231
Stage 1 to 2	53 (52.0)	24 (46.1)	29 (58.0)	
Stage 3 to 4	49 (48.0)	28 (53.9)	21 (42.0)	
Pathology				0.885 <sup>†</sup>
Adenoca	13 (12.8)	7 (13.5)	6 (12.0)	
Adenosquamous	1 (1.0)	-	1 (2.0)	
Scca	88 (86.2)	45 (86.5)	43 (86.0)	
Diabetes mellitus (DM)				1.000 <sup>†</sup>
No	96 (94.1)	49 (94.2)	47 (94.0)	
Yes	6 (5.9)	3 (5.8)	3 (6.0)	
Hypertension (HT)				0.127
No	91 (89.2)	44 (84.6)	47 (94.0)	
Yes	11 (10.8)	8 (15.4)	3 (6.0)	
Dyslipidemia (DLP)				0.495 <sup>†</sup>
No	100 (98.0)	50 (96.2)	50 (100.0)	
Yes	2 (2.0)	2 (3.8)	-	
Chronic kidney disease (CKD)				1.000 <sup>†</sup>
No	101 (99.0)	51 (98.1)	50 (100.0)	
Yes	1 (1.0)	1 (1.9)	-	
Human immunodeficiency virus (HIV)				0.054 <sup>†</sup>
No	98 (96.1)	52 (100.0)	46 (92.0)	
Yes	4 (3.9)	-	4 (8.0)	
Major depressive disorder (MDS)				1.000 <sup>†</sup>
No	101 (99.0)	51 (98.1)	50 (100)	
Yes	1 (1.0)	1 (1.9)	-	
Age at diagnosis (year); mean±SD (min-max)	51.3±11.6 (26 to 87)	52.4±11.3 (28 to 87)	50.2±12.0 (26 to 72)	0.358 <sup>‡</sup>
Age group				0.139
≤40	15 (14.7)	5 (9.6)	10 (20.0)	
>40	87 (85.3)	47 (90.4)	40 (80.0)	
Radioactive material using in brachytherapy				<0.001*
Cesium	20 (19.6)	20(38.5)	-	
Irridium	82 (80.4)	32 (61.5)	50 (100)	
Adjuvant treatment after concurrent chemoradiation therapy and brachytherapy				1.000 <sup>†</sup>
Hysterectomy	-	-	-	
Adjuvant chemotherapy	9 (8.8)	6 (11.6)	3 (6.0)	0.488
Palliative radiation therapy	5 (4.9)	3 (5.8)	2 (4.0)	1
Sequential chemoradiation therapy	3 (2.9)	3 (5.8)	-	0.243

SD=standard deviation

<sup>#</sup> Chi-square test, <sup>†</sup> Fisher's exact test, <sup>‡</sup> Independent t-test, \* Statistical significant if p<0.05

## Toxicities

**Acute toxicities:** Acute grade 1 to 2 hematologic, genitourinary, and skin toxicities were comparable between the 2D and the 3D techniques at 118 and 0.243, respectively (p=0.4950), but gastrointestinal

toxicities were significantly better in the 3D technique group at 4% in 3D and 23.08% in 2D (p=0.003) (Table 2). No grade 3 or 4 hematologic, genitourinary, and skin toxicities were observed in both techniques.

One patient (1.92%, p=1) using the 2D technique

**Table 2.** Acute and late toxicities

	2D; n (%)		3D; n (%)		p-value <sup>#</sup>
	Grade 1 to 2	Grade 3 to 4	Grade 1 to 2	Grade 3 to 4	
<b>Acute toxicities</b>					
Hematology					0.495 <sup>†</sup>
• No	50 (96.2)	-	50 (100)	-	
• Yes	2 (3.8)	-	-	-	
Gastrointestinal					0.0077 (grade 1 to 2)*
• No	39 (75.0)	-	48 (96)	-	1 (grade 3 to 4)
• Yes	12 (23.1)	1 (1.9) (grade 3)	2 (4.0)	-	
Genitourinary					0.118 <sup>†</sup>
• No	48 (92.3)	-	50 (100)	-	
• Yes	4 (7.7)	-	-	-	
Skin					0.243 <sup>†</sup>
• No	49 (94.2)	-	50 (100)	-	
• Yes	3 (5.8)	-	-	-	
<b>Late toxicities</b>					
Hematology					NA
• No	52 (100)	-	50 (100)	-	
• Yes	-	-	-	-	
Gastrointestinal					1 (grade 1 to 2)
• No	42 (80.8)	-	43 (86.0)	-	1 (grade 3 to 4)
• Yes	6 (11.5)	4 (7.7) (grade 3)	7 (14.0)	-	
Genitourinary					0.001 (grade 1 to 2)*
• No	23 (44.2)	-	42 (84.0)	-	1 (grade 3 to 4)
• Yes	26 (50.0)	3 (5.8)(grade 3)	8 (16.0)	-	
Skin					0.495 <sup>†</sup>
• No	50 (96.2)	-	50 (100.0)	-	
• Yes	2 (3.8)	-	-	-	

NA=not analyze

<sup>#</sup> Chi-square test, <sup>†</sup> Fisher's exact test, \* Statistical significant

experienced grade 3 gastrointestinal toxicities but no grade 3 or 4 were observed in the 3D technique group.

**Late toxicities:** No differences were observed in grade 1 to 2 late toxicities between the two techniques regarding hematologic, gastrointestinal, and skin toxicities (p=N/A, 1 and 0.495). Four patients (7.7%) experienced grade 3 gastrointestinal toxicities and three patients (5.77%) experienced genitourinary toxicities in the 2D technique group without statistical significance (p=1). No late grade 3 or 4 toxicity was observed in the 3D technique group. Furthermore grades 1 to 2 genitourinary toxicities were significantly better using the 3D brachytherapy technique at 16% in 3D versus 50% in 2D (p=0.001) such as severe radiation cystitis, urinary obstruction

or hydronephrosis (Table 2).

## Discussion

The present study compared the two techniques of brachytherapy (2D and 3D) in terms of the efficacy and toxicities among patients with locally advanced cervical cancer using definite concurrent chemoradiation. The tandem and ovoid without interstitial needles were used among all patients. Image guided brachytherapy (IGBT) using CT scan was applied in all 3D technique cases.

The overall survival of the present study was better compared to other image guided radiation therapy (IGRT) brachytherapy studies of other centers, while local control and toxicities were comparable (Table 3).

**Table 3.** The overall results of this study compared with other IGRT brachytherapy studies of other centers in aspects of overall survival, local control, and toxicities

Studies	Year	n	Type	Median F/U (month)	Local control 3 year	Overall survival 3 year	Late toxicities (grade 3 to 4)
This study	2019	102	HDR (80.4%)	NR	92.2	2D: 95.7% 3D: 91.8%	Gastrointestinal 7.7% at 3 year Genitourinary 5.8% at 3 year
			LDR (19.6%)				
Netherland <sup>(7)</sup>	2016	126	HDR	36	88	75%	13.4% at 3 year
Retroembrace <sup>(8)</sup>	2016	731	HDR (58.7%)	43	91	79%	4 to 6% at 3 year 11% at 5 year
			PDR (40.4%)				
			LDR (0.9%)				

n=number of population; HDR=high dose rate; LDR=low dose rate; PDR=pulsed dose rate; F/U=follow-up; NR=not reported

### Overall survival

The overall survival was 94.12% at the three-year follow-up, which is better than other data from related studies ranging from 75% to 79%. Between the 2D and the 3D techniques, there seemed to be no overall difference in the survival rate, ranging from 79.6% to 98.9%. Completion of concurrent chemoradiation with acceptable overall treatment time among all patients in the present study might have been related to good outcomes of overall survival. Death from non-cancer causes were twice as much as cancer causes as referred to in the standard treatment of cervical cancer.

### Local control

The overall local control rate was 92.16% for three years. Between the 2D and the 3D techniques, no difference was observed of the three-year local control rate with 2D at 88.59% (74.53 to 95.13) and 3D at 93.33% (80.67 to 97.81). Other studies showed a three-year local control ranging from 78.5% to 97.9%, which was comparable to the present study. Compared with other interstitial needles using brachytherapy studies, no difference in outcome was observed regarding local control rate. Ongoing results from prospective studies using MRI and interstitial needles brachytherapy are still expected.

### Progression free survival

Surprisingly, PFS of the 2D technique from the present retrospective study was significantly better than the 3D technique at 86.13% and 27.4% ( $p=0.006$ ). Because of low event rate and low sample sizes from the present retrospective study, the PFS might not represent the exact survival rate. Using the 2D brachytherapy technique also showed excellent results in PFS.

### Toxicities

The 3D brachytherapy technique showed reduced acute and late grade 3 to 4 toxicities compared with the

2D technique but without statistical significance. The acute gastrointestinal toxicities using 2D was 1.92% and 3D was 0%, the late gastrointestinal toxicities using 2D was 7.7% and using 3D was 0%, and the genitourinary toxicities using the 2D was 5.77% and using the 3D was 0%. Moreover, reduced acute grades 1 to 2 gastrointestinal toxicities and grades 1 to 2 late genitourinary toxicities were observed as significant in the 3D technique compared with the 2D technique group with acute at 4% in 3D and 23.08% in 2D, late at 16% in 3D and 50% in 2D groups.

One study conducted in the Netherlands<sup>(7)</sup>, also compared the 2D and 3D techniques. The difference between the studies was that some patients in the Netherlands' study used interstitial brachytherapy while some patients underwent MRI rather than CT scan in IGRT. However, the results were similar to our studies concerning aspects of overall survival, local control, and toxicities.

The RetroEMBRACE study<sup>(8)</sup> was an IGBT investigation that included patients with IA-IVB cervical cancer. Definitive EBRT +/- concurrent chemotherapy followed by IGBT were all used. The 3 and 5-year local control, pelvic control, cancer specific survival and overall survival were 91 and 89, 87 and 84, 79 and 73 and 74 and 65%, respectively.

According to the oncologic results, local control was similar to the present study. The present study showed better survival, which may have stemmed from including only patients completing definitive CCRT and IGBT. In the RetroEMBRACE study, the IGBT consisted of using CT or MRI scan resulting in 5-year G3 to G5 morbidity of 5%, 7%, and 5% for bladder, gastrointestinal tract, and vagina, respectively. In contrast, the 3D based brachytherapy in the present study used pre-brachytherapy MRI scan, which might have helped identify the exact volume of HR-CTV and IR-CTV and reduce the toxicities but required longer follow-up time in the present study's 3D technique.

The 2D technique represented good results regarding overall survival, local control, and PFS but produce more toxicities compared with the 3D brachytherapy technique. Acute and late toxicities might have been related to the destruction of contemporary or permanent quality of life. Some patients had disease free conditions but may experience side effects for the rest of their lifetime.

However, the present study results should be interpreted with caution because of the retrospective manner and shorter follow-up time of the 3D technique, compared with the 2D technique. While the FIGO staging differed between the era of the 2D and 3D techniques, some variations on the cancer evaluation involved imaging modalities and staging. The present study low event rate was one limitation of the survival and local control comparison between the 2D and 3D techniques suggesting a larger number of patients and a longer follow-up time were needed to investigate the two techniques. Further ongoing multicenter randomized EMBRACE II studies using the most advanced techniques are being used to further exploit the results.

## Conclusion

Among local patients with advanced cervical cancer treated by concurrent chemoradiation followed by brachytherapy, the three-year overall survival rate and local control were similar between the 2D and the 3D techniques while the 2D technique exhibited improved PFS. The 3D brachytherapy technique showed significantly reduced both acute and late toxicities. Because of the retrospective manner and small population of the present study, this constituted the subject of an ongoing prospective EMBRACE II study.

## What is already known on this topic?

Previous systematic review and meta-analysis showed CCRT followed by Brachytherapy as the standard treatment for locally advanced cervical cancer. In the past, 2D brachytherapy was widely used and showed good efficacy in disease control and survival. Nowadays using 3D brachytherapy, using CT or MRI scan, is feasible and safe according to the data from French STIC study. This study used PDR brachytherapy instead of HDR brachytherapy. But HDR brachytherapy is widely used in Thailand. More resources were consuming by using 3D brachytherapy technique.

## What this study adds?

This study is to compare the efficacy and side

effects between 2D and 3D HDR brachytherapy techniques followed by whole pelvic radiation therapy. The Results show similar survival and local control. Nevertheless, the progression free survival is better in 2D technique, which may be caused by low event rates. Reduced toxicities was detected in 3D technique. The conclusion of this study supports that 3D HDR brachytherapy is the efficacious and safe treatment.

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## Author's contributions

Sakyanun P contributed to overall data collection, management of the program, data analysis, writing the manuscript, and management of the study.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## References

1. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999;17:1339-48.
2. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999;340:1137-43.
3. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144-53.
4. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999;340:1154-61.
5. Chassagne D, Dutreix A, Almond P, Burgers JMV, Busch M, Joslin CA. International Commission on Radiation Units and Measurements (ICRU). ICRU Report 38: Dose and volume specification for reporting intracavitary brachytherapy in gynecology. *J ICRU* 2016;os20:1-23.
6. Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Recommendations



- from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006;78:67-77.
7. Derks K, Steenhuijsen JLG, van den Berg HA, Houterman S, Cnossen J, van Haaren P, et al. Impact of brachytherapy technique (2D versus 3D) on outcome following radiotherapy of cervical cancer. *J Contemp Brachytherapy* 2018;10:17-25.
  8. Sturdza A, Pötter R, Fokdal LU, Haie-Meder C, Tan LT, Mazon R, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. *Radiother Oncol* 2016;120:428-33.