Survival outcome of cervical cancer patients treated by image-guided brachytherapy: a ‘real world’ single center experience in Thailand from 2008 to 2018

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(Received 23 February 2022; revised 30 March 2022; editorial decision 15 April 2022)

ABSTRACT

The objective of our study was to evaluate the survival outcome of cervical cancer patients treated using image-guided brachytherapy (IGBT). From 2008 to 2018, 341 patients with cervical cancer were treated by radical radiotherapy. IGBT (by computed tomography [CT] or transabdominal ultrasound [TAUS]) was used to treat all of these patients. The characteristic data and patient status after treatment were recorded. All data were evaluated for survival outcome analysis. From a total of 341 patients, 295 patients were analyzed and 46 patients were excluded due to data missing in the survival outcomes. At the median follow-up time of 48 months (IQR 30–80 months), The 4-year local control, progression-free survival and overall survival rates were 89.5%, 74.9% and 69.1%, respectively. For overall survival, the size (> 5 cm), pathology (non-SCCA), stage (stage III–IV by FIGO 2009), lymph node (LN) (presented) and overall treatment time (OTT) (> 56 days) showed statistical significance in univariate analysis while non-SCCA pathology, advanced stage, presented LN and longer OTT showed statistical significance in multivariate analysis. In conclusion, our analysis reports a 4-year overall survival rate of 69.1%. Non-SCCA pathology, advanced stage disease, LN presence and longer OTT showed worse prognostic factors in multivariate analysis.

Keywords: survival; outcome; cervical cancer; image-guided brachytherapy (IGBT)

INTRODUCTION

Carcinoma of cervix uteri is one of the most common female cancers in Northern Thailand \cite{1}. Radiotherapy (external beam radiotherapy [EBRT] plus brachytherapy [BT]) with platinum-based chemotherapy is the standard treatment for locally advanced disease \cite{2}. After developments in magnetic resonance imaging (MRI) in BT, the concepts of volume-based treatment have been utilized in routine practice since 2005 using concepts of the Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) recommendations \cite{3, 4}. Many clinical studies of image-guided brachytherapy (IGBT) using MRI-guided BT have been published and the latest publication of the EMBRACE-I study showed a 5-year local control and survival rate of 92% and 74%, respectively \cite{5–9}. Computed tomography (CT)-IGBT has also been also used in many institutes. Although CT yields poorer image quality than MRI in overestimation, CT is more easily accessible and can be adapted to reduce normal tissue dose \cite{10}. To date, CT-based guidelines have been published to support this approach \cite{11–13}. Many studies using CT-based BT have been published to support the use of CT in BT practice \cite{14–17}. Transabdominal ultrasound (TAUS) was developed in BT by van Dyk et al. and published clinical studies showed promising results in terms of local control and survival \cite{18–21}.

Our Institute has transformed our brachytherapy service from 2D to 3D brachytherapy in our division since 2008 with the cooperation...
of the University Cooperation platform with Christian-Albrechts-
University, Kiel and Medical University of Vienna [22]. From 2008 to
2018, we developed two research projects in different proposal. CT-BT
project was our forward project to move our department from point-
based planning to volume-based planning. During the transformation,
due to our workload, we could not transform all of our patients to
use volume-based planning at that time. So, at that time, we looked
for the technique to support the adaptive planning for point-based
planning and we found that TAUS-BT was the suitable one. So, TAU-
S-BT project was our supported project to improve our 2D by adaptively
point-based planning during transformation process. After 10 years,
we fully changed to CT-based BT in 2019. We have reported our
experiences in CT and TAUS in international publications [16, 17,
20, 21, 23].

After 10 years of implementation (2008–2018), evaluation of the
survival outcome is one of our objectives. In this study, we evaluate
the survival outcomes of IGBT (by CT and TAUS) in our Institute.

MATERIALS AND METHODS

This retrospective study evaluates the survival outcomes of cervical
cancer patients treated by IGBT in our Institute. This study was
approved by the institutional review board of Faculty of Medicine,
Chiang Mai University with the study code of RAD-2564-08287.

From 2008 to 2018, 341 patients with cervical cancer were treated
by IGBT. There were 176 patients treated by CT-based BT while 165
patients were treated by TAUS-based BT. In our hospital, 3D-BT began
in 2008 with CT-based BT as a research project. Later, another project
to improve the quality of 2D planning by TAUS-guided BT as 2.5D
planning was initiated in 2012. All patients received external beam
radiotherapy from 45 to 50.4 Gy in 23–28 fractions plus four fractions
of IGBT. In presented macroscopic lymph node (LN), the boost ther-
apy to 56–60 Gy was applied as indicated. Extended field radiotherapy
(pelvic plus paraaortic fields) was used for paraaortic LN involvement.
Conventional, three-dimensional conformal, or intensity-modulated
radiation therapy were utilized in our patients as indicated. Weekly
platinum-based regimen (cisplatin; 40 mg/m2 or carboplatin; AUC2)
was prescribed concurrently during external beam radiotherapy. For
BT, all patients received IGBT by CT- or TAUS-based planning tech-
niques (Fig. 1). Pre-BT MRI did not perform in our cohort. To com-
penstate pre-BT MRI, per vaginal examination and TAUS were utilized.
Hybrid intracavitary and interstitial (IC/IS) technique was indicated in
case of big or poor geometry targets (whole cervix and macroscopic
tumor at BT). For pain control, oral Tylenol with codeine was pre-
scribed for the IC approach. In patients who need IC/IS technique,
intravenous pethidine/valium or spinal anesthesia will be used in our
practice. The concept of dose prescriptions and cumulative doses in
both techniques has been described in previous publications [16, 17,
20, 21]. For our planning aims, we keep the cumulative dose (EBRT
plus BT in EQD2) to our target (cervix + macroscopic tumor exten-
sion) to be at least 80 Gy, < 90 Gy for bladder and < 75 Gy for rectum.
For CT-based BT, the target was the D90 of high-risk clinical target
volume (HR-CTV). For TAUS-based BT, the target was generated
from the eight cervix reference points measured by TAUS.

All characteristic data (age, stage, histology, chemotherapy, cumu-
ulative dose in EQD2) were recorded. All patients were traced to the
cancer registry unit to evaluate their updated status (whether dead
or alive). The survival data (from start of treatment to death) were
evaluated.

In statistical analysis, descriptive statistics were used to evaluate
characteristic data. A Kaplan–Meier curve and a log-rank test were
utilized to evaluate the overall survival rate. Univariate and multivariate
analyses were performed to evaluate the prognostic factor. IBM SPSS
version 22 (SPSS Inc., Chicago, Illinois, USA) was used for evaluation.

RESULTS

From 341 patients, 46 patients were excluded because their data were
not recorded in the cancer registry. Consequently, 295 patients were
used for the evaluation. (Fig. 2) Stage IIB (as FIGO 2009) was the
most common with 51.9%. Squamous cell carcinoma (SCCA) was
the most common pathology (85.1%). The median age was 57 years
and 80% of patients were ≤ 65 years old. One-hundred seventy-nine
patients (60.7%) were treated by conventional radiotherapy. Fifty-two
patients (17.6%) had macroscopic LN and 18 patients (6.1%) had
paraaortic LN involvement. Two-hundred fifteen patients (72.9%) rec-
ceived weekly cisplatin as concurrent chemotherapy and 198 patients
(67.1%) received at least four cycles of chemotherapy. The median
cumulative dose to the target was 84.8 Gy in EQD2. Twenty-seven
patients (9.2%) were treated by hybrid IC/IS technique. Patient char-
acteristic data are shown in Table 1.

At the median follow-up time of 48 months (IQR 30–80 months),
The 4-year local control, progression-free survival and overall survival

| Parameters | Details |
|------------|---------|
| Age (median; IQR) | 57 years (50–63 years) |
| Size (median; IQR) | 5 cm (4–6 cm) |
| Up to 5 cm | 186 (85.1%) |
| More than 5 cm | 103 (34.9%) |
| Pathology | |
| Squamous cell carcinoma | 251 (85.1%) |
| Adenocarcinoma | 40 (13.6%) |
| Others | 4 (1.4%) |
| Stage (FIGO 2009) | |
| I | 10 (3.4%) |
| II | 164 (55.6%) |
| III | 114 (38.7%) |
| IV | 7 (2.4%) |
| Macroscopic LN | |
| No | 243 (82.4%) |
| Pelvic LN | 34 (11.5%) |
| Pareaortic LN | 18 (6.1%) |
| IGBT | 149 (50.5%) |
| CT-based | 146 (49.5%) |
| Cumulative Dose in EQD2 to the target (median; IQR) | 84.8 Gy (82.2–89.7 Gy) |
| Overall treatment time (median; IQR) | 56 days (50–64 days) |
Table 2. Uni-variate analyses

| Variables                   | n  | 4-year local control rate (%) | P-value* | 4-year overall survival rate (%) | P-value* |
|-----------------------------|----|-------------------------------|----------|----------------------------------|----------|
| Age (years)                 |    |                               |          |                                  |          |
| up to 65 years              | 238| 89.1                          | 0.666    | 69.3                             | 0.72     |
| More than 65 years          | 57 | 91.2                          |          | 68.4                             |          |
| Size (cm)                   |    |                               |          |                                  |          |
| Up to 5 cm                  | 186| 91.4                          | 0.134    | 76.3                             | 0.004    |
| More than 5 cm              | 103| 86.4                          |          | 55.3                             |          |
| Pathology                   |    |                               |          |                                  |          |
| SCCA                        | 251| 91.6                          | 0.002    | 70.9                             | 0.007    |
| Non-SCCA                    | 40 | 77.3                          |          | 59.1                             |          |
| FIGO Stage                  |    |                               |          |                                  |          |
| Stage I–II (early)          | 174| 93.1                          | 0.013    | 77.0                             | 0.015    |
| Stage III–IV (advanced)     | 121| 84.3                          |          | 57.8                             |          |
| LN                          |    |                               |          |                                  |          |
| Absent                      | 243| 90.5                          | 0.09     | 74.5                             | <0.001   |
| Present                     | 52 | 84.6                          |          | 44.2                             |          |
| Cycles of chemotherapy      |    |                               |          |                                  |          |
| Less than 4 cycles          | 97 | 89.7                          | 0.96     | 67                               | 0.914    |
| ≥ 4 cycles                  | 198| 89.3                          |          | 70.2                             |          |
| Cumulative dose to target   |    |                               |          |                                  |          |
| Up to 84 Gy                 | 143| 85.3                          | 0.022    | 65.0                             | 0.386    |
| > 84 Gy                     | 152| 93.4                          |          | 73.0                             |          |
| BT                          |    |                               |          |                                  |          |
| CT                          | 149| 90.6                          | 0.513    | 73.2                             | 0.31     |
| TAUS                        | 146| 88.4                          |          | 65.1                             |          |
| OTT                         |    |                               |          |                                  |          |
| Up to 56 days               | 139| 94.2                          | 0.010    | 74.8                             | 0.017    |
| More than 56 days           | 156| 85.3                          |          | 64.1                             |          |

Note: BT = brachytherapy, CA = carcinoma, CT = computed tomography, FIGO = The International Federation of Gynecology and Obstetrics, LN = lymph node, OTT = overall treatment time, SCCA = squamous cell carcinoma, TAUS = transabdominal ultrasound; * by log-rank test

Fig. 1. TAUS and CT for BT.
Fig. 2. Kaplan–Meier curve of local control, disease-free survival and overall survival.

In overall survival, the same nine parameters were evaluated. In terms of univariate analysis, the results showed statistical significance in size, pathology, stage, LN and OTT. Details of univariate analysis are shown in Table 2. The Kaplan–Meier curve of age, size, pathology, stage, LN status, chemotherapy cycles, cumulative dose to target, BT and OTT were shown in Fig. 3a–3i. When we evaluated in terms of multivariate-analysis, Cox proportional regression analysis revealed a significant correlation in overall survival to non-SCCA histology, advanced stage, presented LN and longer OTT. All evaluations are shown in Table 3.

DISCUSSION

Nowadays, radiotherapy for cervical cancer has changed a lot in the technology of treatment, especially in BT. After the first clinical study was published in 2007 by Potter et al. [5]. The use of IGBT has developed rapidly using MRI-, CT- or ultrasound-based planning [6, 9, 14, 19, 24]. The latest publications of the EMBRACE-I study...
Fig. 3. Kaplan–Meier curves of overall survival according to: a) age, b) size, c) pathology, d) stage, e) LN status, f) chemotherapy cycles, g) cumulative dose to target, h) BT technique, and i) OTT.
showed promising results of MRI-guided BT with a 5-year local control and overall survival rates of 92% and 74%, respectively [8]. This result showed an improvement from the previous report of the retro-EMBRACE study that showed 5-year overall survival rate of 65% [7]. From the literature, the survival rate for cervical cancer treated by IGBT ranged from 58% to 86% over 3–5 years (Table 4).

Our study reports experiences of IGBT by CT or TAUS in our Institute from 2008 to 2018. For our reported data, the 4-year local control, progression-free survival and overall survival rates were 89.5%, 74.9% and 69.1%, respectively. For local control, our report were close to the results from retro-EMBRACE study (89%) and Narayan et al. (87.5%) but inferior to EMBRACE-I study (92%) [7, 19]. For overall survival, our results are still close to the results from the retro-EMBRACE study (65%), Möller et al. (65%), Ribeiro et al. (65%) and Narayan et al. (65%) but show inferior results to the EMBRACE-I study (74%) [7, 8, 19, 25, 27].

A possible reason of different results from EMBRACE-I study might be that the percentage of stage III patients in the EMBRACE-I study was 15.2% in comparison to 38.7% in our study [8]. However, in our cohort, only FIGO 2009 was evaluated. Additionally, 43% of patients in the EMBRACE-I study used combined IC/IS BT to get dose escalation [8]. From our analysis, 9.2% (27 patients) of our patients were treated by hybrid IC/IS technique at that time. Although the utilization of IC/IS technique in our study was still lower than retro-EMBRACE study (23%), our study showed approximate results in terms of local control and overall survival [7]. After installation of CT in BT unit, we aim that the use of IC/IS technique will increase and this will improve our results in the future.

In our study, nine prognostic parameters (age, size, pathology, stage, presented LN, chemotherapy cycles, cumulative dose to the target, technique of IGBT and OTT) were evaluated in univariate and multivariate analyses. When we evaluated local control, in univariate
Table 3. Multi-variate analyses

| Factor                  | Local control     | Overall survival |
|-------------------------|-------------------|------------------|
|                         | HR   | 95% CI | P-value | HR   | 95% CI | P-value |
| Age > 65                | 0.727 | 0.242–2.184 | 0.571 | 1.374 | 0.831–2.272 | 0.216 |
| Size > 5 cm             | 1.203 | 0.558–2.594 | 0.637 | 1.461 | 0.989–2.158 | 0.057 |
| Non-SCCA                | 3.986 | 1.533–10.365 | 0.005 | 2.411 | 1.440–4.046 | 0.001 |
| FIGO stage III–IV      | 2.330 | 1.067–5.088 | 0.034 | 1.606 | 1.078–2.393 | 0.020 |
| Presented LN           | 1.675 | 0.692–4.050 | 0.253 | 1.886 | 1.204–2.952 | 0.006 |
| ≥ 4 Cycles of chemotherapy | 0.893 | 0.346–2.306 | 0.815 | 0.942 | 0.585–1.516 | 0.806 |
| Cumulative dose to target > 84Gy | 0.33 | 0.131–0.832 | 0.019 | 0.910 | 0.555–1.493 | 0.710 |

Note: BT = brachytherapy, CT = computed tomography, FIGO = The International Federation of Gynecology and Obstetrics, HR = hazard ratio, LN = lymph node, OTT = overall treatment time, SCCA = squamous cell carcinoma, TAUS = transabdominal ultrasound

Table 4. Selected studies of IGBT for cervical cancer

| Study                  | n     | Image     | Local control rate (%) | Survival rate (%) |
|------------------------|-------|-----------|------------------------|-------------------|
| Pötter et al. [8]      | 1341  | MRI       | 92% (5 yr)             | 74% (5 yr)        |
| Möller et al. [25]     | 138   | MRI/CT    | 94.2% (5 yr)           | 65% (5 yr)        |
| Sturza et al. [7]      | 731   | MRI/CT    | 89%(5 yr)              | 65% (5 yr)        |
| Narayan et al. [19]    | 292   | TAUS      | 87.5% (5 yr)           | 65% (5 yr)        |
| Castelnau-Marchand et al. [26] | 225     | MRI/CT | 86.4% (3 yr)     | 76.1% (3 yr) |
| Lindegaard et al. [24] | 140   | MRI       | 91%(3 yr)              | 79% (3 yr)        |
| Pötter et al. [6]      | 156   | MRI       | 95%(3 yr)              | 68% (3 yr)        |
| Pötter et al. [5]      | 145   | MRI       | 85%(3 yr)              | 58% (3 yr)        |
| Ribeiro et al. [27]    | 170   | MRI/CT    | 96%(3 yr)              | 65% (5 yr)        |
| Ohno et al. [14]       | 80    | CT        | 94% (5 yr)             | 86% (5 yr)        |
| Our study              | 295   | CT/TAUS   | 89.5% (4 yr)           | 69.1% (4 yr)      |

Note: CT = computed tomography, MRI = magnetic resonance imaging, TAUS = transabdominal ultrasound, yr = year

Analysis, our results showed statistical significances in pathology (non-SCCA) stage (III–IV), cumulative dose to target (> 84 Gy) and OTT (> 56 days) with trends in LN (present) (Table 2). For multivariate analysis, Cox proportional regression analysis revealed a significant correlation in local control to non-SCCA histology, advanced stage, cumulative dose > 84 Gy and OTT > 56 days (Table 3). In overall survival, size (> 5 cm), non-SCCA histology, advanced stage (III–IV), LN status (presented LN) and OTT (> 56 days) showed statistical significance in univariate analysis (Table 2). When we evaluated using multivariate analysis, non-SCCA histology, advanced stage, presented LN and longer OTT than 56 days were of statistical significance (Table 3). Our analysis is similar to that of Möller et al. which showed that FIGO stage and LN metastases were prognostic factors for cancer-specific survival rates [25].

When we focused on SCCA group (251 patients), the 4-year local control, disease-free survival and overall survival rates were 91.6%, 78.1% and 70.9%, respectively. For overall survival, presented LN showed a significant correlation in overall survival in our analysis (P = 0.045; HR 1.544; 95% CI = 1.011–2.787) while no statistical significance in size (P = 0.055; HR 1.544; 95% CI = 0.991–2.404) and clinical stage (P = 0.158; HR 1.371; 95% CI = 0.885–2.124) was observed.

From our analysis, non-SCCA histology, advanced stage and presented LN were the factors which patients presented before treatment, in contrast to cumulative dose to the target and OTT that we can manage. According to the latest publication by Korenaga et al., completing chemoradiotherapy (standard of care) in the recommended 8 weeks was associated with a superior overall survival in cervical cancer [28]. Consequently, to keep the OTT to be as less as possible is very important to achieve favorable results. Previously, one fraction per week was routinely used in our practice and it caused some patients who had treatment break during EBRT got high tendency to treat longer than 8 weeks. Nowadays, twice-a-week schedule is currently utilized in our hospital and we expect that this will improve our results in the future.

Nonetheless, workload is still important obstacle of twice-a-week schedule. For the cumulative dose to target, cumulative dose (> 84 Gy in EQD2) showed statistical significance in local control in our analysis (P = 0.019) but, unfortunately, not in overall survival (P = 0.710). The plan of our practice to increase cumulative dose to > 84 Gy by
hybrid IC/IS technique was designed after installation of CT in the BT unit.

For the technique of BT, no difference in techniques of IGBT (CT vs TAUS) was observed in terms of local control and survival. However, the trends of BT for cervical cancer shift to hybrid IC/IS technique according to the retro-EMBRACE and EMBRACE I studies [7, 8]. Hybrid IC/IS utilization should increase in practice and the further study of CT-based IGBT vs TAUS-based IGBT in hybrid IC/IS approach is interesting. Nevertheless, the planning system for TAUS-based BT in hybrid approaches is during development [29].

The major limitations of the study are as follows. First, it was a retrospective analysis performed over a relatively long period of time (10 years). Second, short median follow-up time was observed (48 months) because some patients were lost to follow-up at our Institution, especially in this COVID-19 era. However, the strength of the present study is that our cohort contains cervical cancer patients who were treated by IGBT from a single institution and that data could be traced in the cancer registry database. The results of our data (4-year overall survival rate of 69.1%) showed close results to the retro-EMBRACE study (5-year overall survival rate of 65%) and Narayan et al. (5-year overall survival rate of 65%) [7, 19].

Consequently, our analysis showed that 4-year local control, progression-free survival and overall survival rates were 89.5%, 74.9% and 69.1%, respectively. The prognostic factors for local control were non-SCCA histology, advanced stage, cumulative dose > 84 Gy and OTT > 56 days. The prognostic factors for overall survival were non-SCCA histology, advanced stage, presented LN and longer OTT. To increase the cumulative dose by hybrid IC/IS technique and reduce OTT by strictly ‘twice a week’ schedule will be our plan to improve our treatment outcomes in the future.

CONCLUSION
The 4-year overall survival from our experiences was 69.1% closed to the retro-EMBRACE study. Non-SCCA histology, advanced stage, presented LN and longer OTT affected the overall survival in multivariate analysis.

CONFLICT OF INTEREST
The authors declare they have no conflicts of interest.

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