Toxicities and Recurrences after Co-60 High-Dose-Rate Brachytherapy for Cervical Cancer in a Tertiary Government Hospital in the Philippines

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Abstract

Introduction Despite the rising popularity of high-dose-rate (HDR) brachytherapy and use of Co-60 in the country, local data on brachytherapy outcomes are lacking. The study reviewed the incidence of toxicities and recurrences in patients with cervical cancer treated with Co-60 intracavitary HDR brachytherapy in a tertiary government hospital in the Philippines.

Methods Records of patients with cervical cancer who completed external beam radiotherapy (EBRT) and brachytherapy from 2016 to 2018 were reviewed. Patient-related (age, smoking history, body mass index, histology, stage, mass size) and treatment-related (overall treatment time [OTT], EBRT machine used, brachytherapy fractionation, dose prior to midline shielding/central tumor dose [CTD]) parameters were analyzed for possible associations with the incidence of toxicities and recurrences.

Results One hundred and sixty-three patients were identified and reviewed for baseline characteristics. Patients who had inadequate follow-up (<90 days) were excluded in the analysis of outcomes. Among the remaining 132 patients, median follow-up duration was 389 days. Gastrointestinal (GI) and genitourinary (GU) toxicities were present in 19.7% (n = 26) and 1.5% (n = 2), respectively. Recurrence was noted in 31.8% (n = 42). The most commonly involved sites of locoregional and distant recurrence was the uterocervix (n = 16, 59.3%) and para-aortics (n = 42, 31.8%), respectively. CTD was significantly associated with toxicities (p = 0.03), while OTT was borderline significantly associated with recurrence (p = 0.06).

Conclusion We present outcomes of GI and GU toxicities, and locoregional and distant recurrences after chemoradiation and Co-60 HDR brachytherapy in a tertiary government hospital in the Philippines. Our study suggests that CTD was significantly associated with incidence of toxicities, while OTT was weakly associated with recurrence. Interventions should be made to control these factors, especially in high-volume, low-resource cancer centers.

Keywords
- brachytherapy
- cervical cancer
- HDR brachytherapy
- Philippine experience
- radiation oncology

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Introduction

The current standard of care in the management of most cases of cervical cancer is external beam radiotherapy (EBRT) concurrent with chemotherapy and intracavitary brachytherapy.[1,2] Brachytherapy allows for tumor dose escalation while limiting the dose received by organs-at-risk (OARs), such as the bladder and the rectum.[3] When added to EBRT, brachytherapy improves primary complete remission, survival, and recurrence rates for patients with cervical cancer.[4]

High-dose-rate (HDR) brachytherapy has superseded low-dose-rate (LDR) brachytherapy over the last decade since the former permits treatment in the outpatient setting, limits radiation exposure to the staff, and allows for optimization for a more conformal dose distribution, which is appropriate in the era of image guidance, among many other advantages.[5] However, the optimal fractionation regimen for HDR brachytherapy, which employs the use of multiple hypofractionated radiotherapy fractions, remains unsettled. From a radiobiological perspective, more hypofractionated regimens are expected to produce more late effects. In 1991, Orton et al concluded that fractionation in HDR brachytherapy significantly influenced toxicities. Complication rates were significantly higher in regimens that utilized >7 Gy per fraction as compared with those that used otherwise.[6] Some of the regimens listed by the American Brachytherapy Society (ABS) guidelines are 7 Gy × 4, 6 Gy × 5, 5 Gy × 6, and 5.5 Gy × 5 fractions,[7] although a wide practice variation exists internationally.[8]

Toxicities arising from chemoradiation (CRT), including brachytherapy, are primarily gastrointestinal (GI) and genitourinary (GU) by virtue of proximity of these organs to the cervix. To lessen the risk of GI and GU toxicities, the ABS recommends a cumulative dose limit of ≤75 Gy to the rectum and the sigmoid, and ≤90 Gy to the bladder in the delivery of a 2-Gy-radiobiologically equivalent (EQD2) cumulative radiotherapeutic dose of 80 to 90 Gy to the tumor.[7] In a pooled analysis of clinical outcomes for HDR brachytherapy for cervical cancer by the American Brachytherapy Task Group, the range of toxicities after CRT was 1 to 11% for late GI and 2 to 20% for late GU toxicities. For the late gynecologic toxicity, only 1 of the 16 prospective trials reported 9% for CRT effects.[9]

Iridium 192 (Ir-192) is among the most commonly used radioisotopes in HDR brachytherapy for cervical cancer due to its small size and high specific activity. Most trials on the safety and efficacy of HDR brachytherapy in the treatment of cervical cancer utilized Ir-192 as the brachytherapy radioisotope. One of the disadvantages in using Ir-192, however, is its relatively short half-life, which warrants replacement every 74.3 days.[3] The recent availability of cobalt 60 (Co-60) sources with the same geometric and dosimetric properties as the more traditional Ir-192 sources makes the former an option in HDR brachytherapy and is more appropriate in low-resource brachytherapy facilities where frequent and timely procurement of radioisotopes could be a problem. Limited studies on the use of Co-60 sources in HDR brachytherapy for cervical cancer are, however, available in the literature.[10]

Objective

The study aimed to review and report the incidences of GI and GU toxicities and recurrences in patients with cervical cancer who were treated with intracavitary HDR brachytherapy using a cobalt-60 remote afterloading system between September 2016 and September 2018 in a tertiary hospital in the Philippines.

Specifically, the study aimed to:

- Determine the incidence of GI and GU toxicities.
- Determine the incidence of recurrences after brachytherapy.
- Determine the overall treatment time (OTT) of patients with cervical cancer in the brachytherapy unit of our institution, defined as days elapsed from first day of EBRT to last fraction of brachytherapy.
- Determine the institutional treatment gap between the last day of EBRT and first fraction of brachytherapy, if any.
- Analyze the relationship between patient-related (i.e., smoking history, body mass index) and treatment-related (i.e., OTT, EBRT machine use, use of midline shielding, brachytherapy fractionation scheme used) factors, and occurrence of recurrences and toxicities.

Significance

This study was undertaken to provide baseline institutional data on the incidence of GI and GU toxicities and recurrences in patients with cervical cancer treated with intracavitary HDR brachytherapy using a cobalt-60 remote afterloading system. The results can establish the safety of using cobalt-60 instead of the more popularly used iridium-192. This is important in low-resource, high-volume radiotherapy facilities since cobalt-60 has a longer half-life and will thus require less frequent procurement of sources. The results can also guide future institutional policies to streamline brachytherapy services and to improve the oncologic outcomes of patients with cervical cancer.

Methods, Study Design, and Sampling

A case–control study design was employed to clarify any association between the treatment (HDR brachytherapy) and the outcomes, as well as other potential risk factors (e.g., age, duration of treatment). Prior to its implementation, the study secured approval from the institutional research ethics board.

All women with biopsy-confirmed cervical cancer who underwent HDR brachytherapy from September 2016 until September 2018 (period of 2 years) in our institution were included in the study. The inclusion and exclusion criteria are listed in ►**Table 1**. Selecting all patients within the period of observation was done to ensure the representativeness of the sample and reduce the possibility of selection bias, since

Table 1 Criteria for patient selection

Inclusion	Exclusion
Biopsy-confirmed squamous cell carcinoma or adenocarcinoma of the cervix	Systemic metastases at time of diagnosis (stage IVB)
Stage I–III by FIGO 2009 staging	Documented invasion of bladder or rectum (stage IVA)
Age at initial diagnosis between 19 and 80 years	Recurrent cervical cancer at baseline
Patients under the charity service of UP-PGH	Previous pelvic surgery
Underwent concurrent chemoradiation (pelvic EBRT ± para-aortic coverage, concurrent with cisplatin) for cervical cancer	Previous chemotherapy or radiotherapy
Underwent HDR brachytherapy and completed the number of intended fractions	Underwent LDR brachytherapy
	Patients who did not complete their prescribed number of brachytherapy fractions
	Documented uterine perforation at the time of brachytherapy

Abbreviations: EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; HDR, high-dose-rate; LDR, low-dose-rate; UP-PGH, University of the Philippines-Philippine General Hospital.

there were no local data available at that time to ascertain the association between the exposure and outcomes. A chart review was conducted to collect data on clinical parameters listed in ►**Table 2**. Toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE)[11] version 5.0 (►**Supplementary Material 1**, available in the online version).

After extracting the data from the patient charts, information was manually entered into an electronic spreadsheet file, and subsequent data processing and analysis were performed using the software Stata 13. Descriptive statistics was used for continuous variables, such as age and body mass index,[12] and median and interquartile ranges were reported to describe follow-up duration, dose of midline shielding, and duration of treatment. Reporting frequencies and percentages was done for categorical data variables, such as disease stage, smoking status, EBRT machine used, brachytherapy fractionation scheme, and planning technique.

Proportions per categories of the qualitative variables, such as presence of GU and/or GI toxicities, local or distant recurrences, and deaths, were computed. Point and interval estimates of these proportions were also determined. To determine exposure-specific proportions, participants who previously had clinical and treatment risk factors were further divided between those who developed the toxicities and otherwise. Odds ratios were computed for association of HDR brachytherapy exposure and outcomes of interest. A series of multiple logistic regression modeling procedures were done mainly with the adjustment for probable confounders to be

Table 2 Study parameters retrieved from the charts

	Study parameters	Definition in this study
Primary	Gastrointestinal toxicities	As per CTCAE v5.0 (►**Supplementary Material 1**, available in the online version)
	Genitourinary toxicities	As per CTCAE v5.0 (►**Supplementary Material 1**, available in the online version)
	Local recurrence	Recurrence limited to uterus, cervix, vulvovaginal, regional lymph nodes, rectum, and bladder
	Distant recurrence	Recurrence to distant organ sites
Secondary	OTT	Elapsed calendar days from day 1 EBRT to last fraction of HDR brachytherapy
	EBRT and brachytherapy interval	Elapsed calendar days between last fraction of EBRT to first fraction of HDR brachytherapy
	EBRT machine used	Cobalt or LINAC
	Midline shielding	Block placed after a certain dose of EBRT to limit dose to the bladder and rectum
	Brachytherapy fractionation	Prescribed dose per fraction and number of brachytherapy fractions
	Smoking history	Yes (current or previous smoker) No (no history of smoking)
	Body mass index	Weight (kg)/height^2 (m^2) Cut-offs for BMI categories (Hsu et al[12]) <18.5: underweight 18.5–22.9: normal 23–26.9: overweight ≥27: obese
	Tumor persistence	Persistence of disease despite treatment, without evidence of remission

Abbreviations: BMI, body mass index; CTCAE, Common Terminology Criteria for Adverse Events; EBRT, external beam radiotherapy; HDR, high-dose-rate; LINAC, linear accelerator; OTT, overall treatment time.

conducted using select clinical variables based on the literature through the backward elimination process. An arbitrary cut-off of a change in the *p*-value less than 0.25 was used to screen for probable confounders. The level of significance for all sets of analysis was set at $p < 0.05$ using two-tailed comparisons. Significance levels were adjusted for multiple comparisons performed, when necessary, using the Fisher–Hayter post hoc method.

Results

A total of 174 patients who fit the inclusion criteria of the study received HDR intracavitary brachytherapy as part of their management for cervical cancer. Eleven patient charts were missing and not retrievable. The remaining 163 patient charts were reviewed for baseline patient-related (►**Table 3**)

Table 3 Baseline characteristics of the study population (n = 163)

Characteristics	Summary measures
Median age at diagnosis (y)	47 (20–73)
Smoking status	
Nonsmokers	133 (81.60%)
Smokers/ex-smokers	30 (18.40%)
Body mass index	
Normal	73 (45.34%)
Underweight	20 (12.42%)
Overweight	31 (19.25%)
Obese	37 (22.98%)
Histologic diagnosis	
Adenocarcinoma	41 (25.15%)
Squamous cell carcinoma	122 (74.85%)
Size of mass on initial internal examination (cm)	6 ± 1.66 (1–12)
Cervical cancer stage	
IB	1 (0.61%)
IB1	2 (1.23%)
IB2	6 (3.68%)
IIA1	4 (2.45%)
IIA2	7 (4.29%)
IIB	93 (57.06%)
IIIB	50 (30.67%)

and treatment-related (►**Table 4**) characteristics. Although this represented only 82% of the computed sample size, which could be attributed to missing records and treatment variations, post hoc analyses revealed that the power accrued remained at 80%.

The median age at diagnosis was 47 years (range: 20–73 years). Majority of the patients were nonsmokers (n = 133, 81.6%). Most patients had normal baseline body mass index (n = 73, 45.34%). Majority of the patients had squamous cell carcinoma histology (n = 122, 74.85%). The average pretreatment size of the cervical mass was 6 ± 1.66 cm. The most common stage was IIB (n = 93, 57.06%), followed by IIIB (n = 50, 30.67%).

Almost two-thirds of the patients received external beam irradiation via cobalt teletherapy (n = 107, 66.05%), with the rest treated via a linear accelerator (n = 55, 33.95%) (►**Table 4**). The median central dose was 4,600 cGy (range: 4,000–5,400 cGy). For brachytherapy, most patients underwent a 7 Gy × 4 fractionation scheme (n = 109, 82.58%), while the rest underwent an 8 Gy × 3 fractionation scheme (n = 23, 17.42%). The median number of days elapsed during EBRT was 49 days (range: 21–160), while the median number of days between EBRT and brachytherapy was 57 days (range: 0–447). The median number of days elapsed to complete the brachytherapy course was 18 days (range: 10–59). The median OTT was 129 days (range: 63–541).

Patients who were unable to complete the institutionally mandated 90-day follow-up were excluded from analysis

Table 4 Treatment characteristics of the study population (n = 163)

Characteristics	Summary measures
EBRT	
Cobalt-60 teletherapy machine (Co-60)	107 (66.05%)
LINAC	55 (33.95%)
Median central dose (cGy)	4,600 (4,000–5,400)
Fractionation regimen used	
8 Gy × 3 fractions	23 (17.42%)
7 Gy × 4 fractions	109 (82.58%)
Median number of days at EBRT	49 (21–160)
Median EBRT and brachytherapy interval (d)	57 (0–447)
Median number of days elapsed at brachytherapy	18 (10–59)
Median overall treatment time (d)	129 (63–541)

Abbreviations: EBRT, external beam radiotherapy; LINAC linear accelerator.

Table 5 Proportion of treatment outcomes (n = 132)

Outcomes	Frequency (%)	95% confidence interval
Median follow-up (d): 389 (95–900)		
Treatment toxicities		
Gastrointestinal	26 (19.70%)	
Gr. 1	5 (3.79%)	1.24–8.62
Gr. 2	14 (10.61%)	5.92–17.15
Gr. 3	7 (5.30%)	2.16–10.62
Genitourinary	2 (1.52%)	0.07–5.70
Gr. 1	0 (0.0%)	
Gr. 2	2 (1.52%)	0.07–5.70
Gr. 3	0 (0.0%)	
Recurrences	42 (31.82%)	23.99–40.49
By location		
Locoregional	14 (10.61%)	5.92–17.15
Distant	17 (12.88%)	7.68–19.82
Simultaneous local and distant	11 (8.33%)	4.23–14.42
By stage		
IB	1 (0.76%)	0.02–4.15
IIA	5 (3.79%)	1.24–8.62
IIB	21 (15.91%)	10.13–23.28
IIIB	15 (11.36%)	6.50–18.05
Tumor persistence	9 (6.82%)	3.16–12.55

of outcomes (n = 31). Among the remaining 132 patients (►**Table 5**), median follow-up was 389 days (range: 95–900). A total of 26 patients (19.70%) experienced GI toxicities, while

Table 6 Distribution of treatment failure sites

Sites	Frequency (%)
Locoregional involvement	27
Ovaries	1 (3.70%)
Uterocervix	16 (59.26%)
Vulvovaginal	2 (7.41%)
Pelvic nodes	6 (22.22%)
Rectosigmoid	1 (3.70%)
Bladder and rectosigmoid	1 (3.70%)
Distal involvement	26
Bones	4 (15.38%)
Lung involvement (total)	9 (34.62%)
Lungs only	5 (19.23%)
Lungs and liver	2 (7.69%)
Liver involvement (total)	3 (11.54%)
Liver only	1 (3.85%)
Para-aortic involvement (total)	11 (42.31%)
Para-aortics only	7 (26.92%)
Para-aortics and liver	1 (3.85%)
Para-aortics and lung	2 (7.69%)
Para-aortics and supraclavicular node	1 (3.85%)
Supraclavicular node involvement (total)	4 (15.38%)
Supraclavicular node only	3 (11.54%)

2 patients (1.52%) experienced GU toxicities (►**Table 5**). Recurrence occurred in 42 (31.82%) of these patients, with 14 (10.61%) recurring locoregionally, 17 (12.88%) recurring distantly, and 11 (8.3%) occurring both locoregionally and distantly. Nine patients (6.52%) had tumor persistence despite treatment.

Sites of locoregional and distant failure are shown in ►**Table 6**. The uterocervical region was the most common site of locoregional recurrence (n = 16, 59.26%), followed by pelvic nodal (n = 6, 22.22%) and vulvovaginal recurrence (n = 2, 7.41%). The para-aortic nodal region was the most common site of distant failure (n = 7, 26.92%). When combined with those with simultaneous failure at other organ sites, the total incidence of para-aortic involvement was 42.31% (n = 11) of all cases of distant recurrence. The lungs were the second most commonly involved distant site (n = 9, 34.62%).

Based on unadjusted logistic regression, there were no notable associations between the clinically important variables and the occurrence of GI and/or GU toxicities. On adjusted measures, a high central dose was significantly associated with the presence of toxicities (p = 0.03) (►**Table 7**).

There were also no notable associations between the clinically important variables and treatment failure, although a longer treatment time seemed to be weakly associated (p = 0.06) with higher treatment failure (►**Table 8**).

Discussion

Toxicities

GI and GU toxicities are expected complications after pelvic irradiation for treatment of gynecologic malignancies,[13] but the reported incidence varies widely.

In a retrospective study by Chen et al,[14] 29.7% of 128 patients with cervical cancer who received three to four fractions of 5 to 7.2 Gy, prescribed to point A, developed late rectal complications after a median follow-up of 43 months. Although our study showed a lower incidence of GI toxicity (19.7%) than the study of Chen et al, the latter had a longer median follow-up duration than our study (389 days or 13 months), therefore having a longer opportunity to observe for late toxicities.

Stewart and Viswanathan[15] systematically reviewed the outcomes of studies that performed HDR brachytherapy prescribed to point A in stage I to III patients with cervical cancer. The rates of grade 3 to 5 late bowel and bladder complications were 0.4 to 10% and 1.4 to 25.6% in prospective and retrospective series, respectively. Our study revealed an incidence of 5.3% grade 3 to 5 GI and no grade 3 to 5 GU toxicities, which is within (GI) and below (GU) the range reported by Stewart and Viswanathan. It must be noted, however, that the highest incidence of toxicities in the above series was reported by the study of Hsu et al,[16] and was observed in the population arm that received six twice-per-day fractions of 7 Gy, which has a higher radiobiologically equivalent total dose than the predominant regimen of four fractions of 7 Gy seen in our study.

In the study of Das et al,[17] 286 patients with cervical cancer were evaluated for toxicities and recurrences after receiving a central tumor dose of 40 Gy via Co-60 teletherapy and 21 Gy (7 Gy × 3 fractions) to point A via Ir-192 HDR brachytherapy. In this study, 21.5% of patients developed grade 1 to 3 rectal complications, with a peak onset at 3 months, while 5.2% of patients developed grade 1 to 3 bladder complications, which occurred at a later period of 10 to 24 months after brachytherapy. These rates may seem to be the same with the findings of our study, but majority of the rectal toxicities in the study of Das are grade 1 (17.9%) versus the predominant grade 2 rectal toxicities (10.6%) seen in our study.

A pooled analysis on brachytherapy studies published between 2000 and 2015 in the United States was recently done by Mayadev et al[9] for the American Brachytherapy Task Group. It included 16 prospective and 51 retrospective studies that focused on survival outcomes, and 13 retrospective studies that focused on toxicity outcomes. The rates of late grade 3 GI (5.3%) and grade 3 GU (0%) in our study are within the range of late grade 3 GI and lower than the range of GU toxicities in the study of Mayadev et al, which was at 1 to 11% and 2 to 20% for GI and GU toxicities, respectively.

In our study, central tumor dose, given as a result of midline shielding, was found to be significantly associated with presence of toxicities. This might be because most of the patients underwent EBRT via Co-60 teletherapy (n = 107, 66.05%) delivered via two-dimensional conventional technique. Midline shielding or blocking has been traditionally used

Table 7 Crude and adjusted odds ratios of genitourinary and gastrointestinal toxicities in association with patient- and treatment-related characteristics

	Unadjusted measures		Adjusted measures	
	Odds (95% CI)	*p*-Value	Odds (95% CI)	*p*-Value
Patient-related factors				
Age at diagnosis	1.03 (0.98–1.07)	0.24	1.03 (0.98–1.09)	0.49
History of smoking	0.30 (0.07–1.36)	0.12	0.08 (0.01–7.39)	0.26
Body mass index				
Normal	1.00		1.00	
Underweight	1.04 (0.29–3.73)	0.95	0.50 (0.10–2.50)	0.39
Overweight	0.68 (0.20–2.35)	0.32	0.79 (0.19–3.26)	0.75
Obese	1.02 (0.34–3.07)	0.43	2.27 (0.59–8.66)	0.23
Histologic diagnosis				
Adenocarcinoma	1.00		1.00	
Squamous cell carcinoma	1.99 (0.63–6.25)	0.24	1.70 (0.45–6.45)	0.44
Cervical cancer stage				
Stage I	1.00		1.00	
Stage II	0.89 (0.09–8.50)	0.92	0.33 (0.02–4.43)	0.41
Stage III	1.21 (0.12–12.12)	0.87	0.47 (0.03–7.32)	0.59
Baseline internal examination	0.94 (0.72–1.22)	0.64	0.73 (0.50–1.08)	0.12
Treatment-related factors				
Overall treatment time	1.00 (0.99–1.01)	0.60	0.99 (0.98–1.01)	0.28
Number of days at brachytherapy	1.01 (0.95–1.07)	0.74	1.07 (0.99–1.16)	0.09
EBRT machine used				
Co-60	1.00		1.00	
LINAC	1.10 (0.45–2.70)	0.83	0.64 (0.19–2.14)	0.47
Number of fractionations	0.82 (0.27–2.48)	0.73	0.47 (0.12–1.84)	0.28
Central tumor dose given	1.00 (0.99–1.00)	0.13	1.00 (1.00–1.01)	0.03

Abbreviations: EBRT, external beam radiotherapy; LINAC linear accelerator.

during conventionally planned pelvic EBRT to boost the parametria while sparing the sigmoid, rectum, and bladder. With the advent of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy, however, the value of midline shielding in sparing the relevant OARs is being questioned.[18]

A review of records of 3,489 International Federation of Gynecology and Obstetrics (FIGO) stage I and II patients with cervical cancer, who received EBRT and LDR brachytherapy at MD Anderson Cancer Center, found smoking history to be a significant predictor of bladder, small bowel, and rectal complications, while thin physique and obesity were associated with an increased risk of GI and bladder complications, respectively.[19] In our study, presence of toxicities was not significantly associated with either smoking history or body mass index.

Recurrences

Prior to our study, Tagal et al (C.J. Tagal, MD, unpublished data, December 2018) already performed a retrospective review of recurrent cervical cancer cases from January 2012 to December 2016 in the same institution as in our study. The brachytherapy facility of this institution, however, started its shift from Cs-137 LDR brachytherapy to Co-60 HDR brachytherapy in September 2016, and thus the population in the study of Tagal et al was mainly treated with LDR brachytherapy after EBRT. We listed some differences between the two studies in ►**Table 9**.

The median OTT in the study of Tagal et al was 77 days, which was shorter than the median OTT of 129 days of our study. This difference might be a consequence of HDR brachytherapy being multifractional and thus requiring more days to be completed. Both studies had the para-aortics as the most common site of distant recurrence, although our study had a lower incidence of para-aortic metastases (►**Table 9**).

In the aforementioned study of Das et al,[17] with a median follow-up of 13 months, 25.4% of patients had locoregional recurrence, while 1.9% developed distant metastasis after a median time of 19 months. The most common site of local failure was the pelvis, while the most common site of distant failure was the lung. Although the doses delivered during EBRT and brachytherapy were lower in the study of Das et al

Table 8 Crude and adjusted odds ratios of recurrence in association with patient- and treatment-related characteristics

	Unadjusted measures		Adjusted measures	
	Odds (95% CI)	*p*-Value	Odds (95% CI)	*p*-Value
Patient-related factors				
Age at diagnosis	1.00 (0.97–1.04)	0.80	1.00 (0.96–1.04)	0.93
History of smoking	1.23 (0.49–3.08)	0.65	1.16 (0.43–3.13)	0.77
Body mass index				
Normal	1.00		1.00	
Underweight	1.64 (0.56–4.79)	0.37	2.22 (0.65–7.57)	0.20
Overweight	0.59 (0.20–1.68)	0.32	0.62 (0.19–2.04)	0.43
Obese	1.45 (0.58–3.60)	0.43	1.47 (0.52–4.10)	0.47
Histologic diagnosis				
Adenocarcinoma	1.00		1.00	
Squamous cell carcinoma	1.01 (0.44–2.33)	0.97	1.04 (0.40–2.70)	0.94
Cervical cancer stage				
Stage I	1.00		1.00	
Stage II	2.46 (0.27–22.02)	0.42	2.32 (0.23–23.42)	0.47
Stage III	2.96 (0.32–27.67)	0.95	2.07 (0.19–23.01)	0.59
Baseline internal examination	1.13 (0.91–1.40)	0.28	1.20 (0.93–1.54)	0.17
Treatment-related factors				
Overall treatment time	1.01 (1.00–1.02)	0.10	1.01 (1.00–1.02)	0.06
Number of days at brachytherapy	1.02 (0.97–1.07)	0.52	0.99 (0.92–1.06)	0.74
EBRT machine used				
Co-60	1.00		1.00	
LINAC	0.84 (0.39–1.83)	0.67	1.01 (0.41–2.49)	0.98
Number of fractionations	2.17 (0.75–6.29)	0.15	2.22 (0.68–7.28)	0.19
Central tumor dose given	1.00 (0.99–1.01)	0.35	1.00 (0.99–1.00)	0.77

Abbreviations: EBRT, external beam radiotherapy; LINAC linear accelerator.

Table 9 Differences between the two retrospective studies in the study institution

Parameters	Tagal et al, 2018	Cereno et al, 2019 (current study)
Population (*n*)	59	163[a]/132[b]
Age at diagnosis (y)	47 (average)	47 (median)
Average pretreatment size of cervical mass (cm)	5	6
Median overall treatment time (d)	77	129
Number of recurrent cases	59	53
Recurrence occurring at locoregional sites	47 (79.66%)	27 (50.94%)
Recurrence occurring at distant sites	35 (59.32%)	26 (49.06%)
Recurrence involving the para-aortic lymph nodes	21 (35.59%)	11 (20.75%)

[a]Sample size for the descriptive parameters.
[b]Sample size for the analytic parameters.

than the doses delivered in our institution, their recurrence rates are lower than those in our study. The former study, however, was not able to report on their OTT, which was found to be suboptimal in our study (median of 129 days).

Prolonged OTT has long been established as associated with inferior local control and survival, with the ideal duration being 8 weeks or 56 days.[20] Among all patient- and treatment-related factors in our study, OTT was weakly associated with presence of recurrence. It should be noted, however, that none of the included patients was able to satisfy the ideal OTT of 56 days.

Conclusion and Recommendations

We report institutional outcomes on toxicities and recurrences after HDR brachytherapy in patients with cervical cancer. Our study suggests that central tumor dose, as a result of midline shielding, is significantly associated with toxicities, while OTT is weakly associated with recurrence. This study also demonstrates the safety of using cobalt-60 sources for HDR brachytherapy.

To our knowledge, this is the first study to formally report on local brachytherapy outcomes in the Philippines. Efforts should be made to manage outcome biases, such as prolonged OTT, in future researches and policies in low-resource, high-volume brachytherapy centers in the country.

Note

All data generated and analyzed during this study are included in this published article and ►**Supplementary Materials 1 and 2** (available in the online version).

Conflict of Interest

None declared.

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