A retrospective analysis on treatment and survival outcome of locally advanced cervical cancer with or without brachytherapy: A single institution study*

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ABSTRACT

Background: Concurrent chemoradiotherapy composed of pelvic external beam radiotherapy (PEBRT) with weekly chemotherapy plus intracavitary brachytherapy (ICBT) remains to be the treatment of choice for locally advanced cervical cancer (LACC). However, some patients are not suitable to have ICBT right after pelvic radiation. Locally, active chemotherapy is being given to these patients until they can undergo the procedure.

Objective: The aim of the study was to determine the impact of ICBT in the treatment and survival outcomes of cervical cancer and to compare it with active chemotherapy.

Methodology: This was a retrospective study of patients with LACC treated with or without brachytherapy in a single institution from January 2002 to December 2017.

Results: The 5-year over-all survival (OS) and 5-year recurrence free survival (RFS) of patients with ICBT were both significantly improved compared to those without ICBT (p=0.001 and p=0.038), respectively. Factors that were significantly correlated with adequate response for brachytherapy were non-squamous cell histology (OR 0.65, CI 0.46-092, p=0.016), initial tumor size of > 5cm (OR 0.41, CI 0.26-0.65, p=0.001), > 50% decrease in the original tumor size at the middle part of PEBRT (OR 1.83, CI 1.2-2.8, p=0.005), > 3 cycles of chemotherapy as radiosensitizers (OR 2.66, CI 1.79-3.9, p=0.001), > 45 days duration of PEBRT (OR 0.63, CI 0.41-0.97, p=0.04) and > 2 episodes of anemia during PEBRT (OR 0.67, CI 0.52-0.85, p=0.001).

Conclusion: Brachytherapy offers significant improvement on tumor control and over-all survival for patients with LACC. Active chemotherapy may offer some benefit in terms of delaying tumor recurrence or progression. However, this did not translate to survival impact if the patient was not able to have brachytherapy at all.

Keywords: active chemotherapy, brachytherapy, locally advanced cervical cancer

INTRODUCTION

Cervical cancer remains to be the 4th most prevalent cancer in females globally. In the Philippines, it is the 2nd most common cancer among females and is also the 2nd leading cause of female cancer deaths.[1]

Majority of patients are diagnosed at advanced stage and are already inoperable. While radical hysterectomy is the standard treatment for early staged cervical malignancy, the standard definitive treatment for patients with Locally Advanced Cervical Cancer (LACC) is pelvic external beam radiotherapy (PEBRT) with weekly chemotherapy as radiosensitizer plus intracavitary brachytherapy (ICBT).[2-4]

Brachytherapy is a well-established integral component in the standard treatment for cervical cancer patients receiving radiotherapy.[3] After pelvic radiation has delivered adequate high doses to pelvic lymph nodes and parametria for control of regional micrometastasis, brachytherapy is considered as the gold standard technique to deliver boost radiation dose to the tumor.[4] The unique anatomical location of cervical tumors makes it a superior delivery method compared to any other historic external-based techniques.[3] Furthermore, a study by Lanciano et al in 1991 stated that the only treatment factor associated with improved pelvic control of disease on multivariate analysis was the use of intracavitary radiation. This study ascertained that by using brachytherapy, there is improvement in radiation outcomes in terms of reduced recurrence and better over-all survival outcomes for patients with LACC compared to having PEBRT alone.[5-7]

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However, a number of patients are not good candidates to undergo ICBT due to several anatomic or medical conditions. A prerequisite for brachytherapy is that the lesion can be covered with the target volume without exceeding toxic doses to nearby organs.[4] This posts an additional challenge in the management of cervical cancer, specially for large volume and asymmetric tumors. Developments including 3D image guided brachytherapy (IGBT) and combining ICBT with interstitial brachytherapy have been focused on overcoming these problems.[4] In more developed countries, modern EBRT techniques such as Intensity Modulated Radiation Therapy (IMRT) or Sterotactic Body Radiation Therapy (SBRT) are being used to deliver pelvic boost to shrink the tumor of patients when brachytherapy is not feasible. But there are still no published study directly comparing SBRT or IMRT and brachytherapy.[5,6,8,9]

In our local setting, Complete Radiation Therapy (CRT), which is composed of PEBRT followed by ICBT, ideally with weekly chemotherapy as radiosensitizer, is the standard treatment for LACC. Tumors which are <4 cm in size with no parametrial involvement are considered suitable for brachytherapy. However, the procedure is deemed not feasible if after receiving 45 Gy to 50 Gy PEBRT, there is persistence of massive bulky lesion (> 4 cm) due to insufficient tumor regression, lateral parametrial extension not accessible to interstitial implant, or both. Other reasons are anatomical problem that prevent applicator placement such as irregularly shaped tumor, stenotic vagina or other uterine malformations, patient's refusal due to the invasiveness of the procedure or discomfort, or other medical condition prohibiting anesthesia.[3,4,6,8]

Due to the unavailability of EBRT boost and other modern radiation techniques, if a patient is assessed to have a persistent bulky tumor or parametrial extension after PEBRT, or other reasons when ICBT is considered not possible, active chemotherapy using Cisplatin or Carboplatin with Paclitaxel every 3 weeks until brachytherapy is suitable, is instead being given. Ideally, Paclitaxel for active chemotherapy is given over 24-hour infusion. But due to enormous number of cancer patients receiving treatment, admission of these patients is not feasible and chemotherapy is instead being done as out patient basis.

There are no known local studies assessing the use of active chemotherapy as treatment option for cervical cancer patients who are not suitable for brachytherapy after PEBRT. The aim of this study is to analyze the treatment and survival outcomes of patients with LACC using this treatment protocol in a single institution.

OBJECTIVES

General:

To compare the survival and treatment outcomes of patients with LACC treated with PEBRT with weekly chemotherapy followed by brachytherapy to those who did not have brachytherapy

Specific:

1. To compute for the 5-year over-all survival (OS) of cervical cancer patients who were able to undergo brachytherapy after PEBRT with weekly chemotherapy and compare it to those who did not have brachytherapy
2. To compute for the 5-year recurrence-free survival (RFS) of cervical cancer patients who were able to undergo brachytherapy after PEBRT with weekly chemotherapy and compare it to those who did not have brachytherapy
3. To determine the different treatment factors during PEBRT associated with adequate response for brachytherapy including the disease stage, tumor histology, tumor size before and at the middle part of treatment, duration of pelvic radiation in days, cycles of chemotherapy received, and presence of anemia during PEBRT

MATERIALS AND METHODS

This was a retrospective study approved by the Institutional Review Board which included all LACC patients treated with primary radiotherapy. The study included patients diagnosed with Stage IIB – IVA cervical cancer using the 2009 International Federation of Gynecology (FIGO) staging treated with PEBRT with weekly chemotherapy as radiosensitizer with or without brachytherapy from January 2002 - December 2017 at the same institution. Retrieval and review of medical records were done.

Definition of Terms:

1. Forms of Treatment
   A. External Beam Radiation PEBRT was given to all patients using either the Linear Accelerator or Cobalt Machine. A four-field box technique was standard, though there were some variations in the number of field used per patient. Protocol for PEBRT included giving a total of 50 Gy to the whole pelvis covering the cervix, uterus, superior part of the vagina, parametric tissue and iliac lymph nodes with daily fraction of 1.8-2 Gy per fraction from Monday to Friday. Midline shield was started after 40 Gy and parametrial boost of 10 Gy was given as needed.

B. Brachytherapy
Brachytherapy was given at a high dose rate technique using tandem and ovoids. The usual dose was 39.6 Gy at point A, at 7 Gy per fraction, at a frequency of one fraction per week for 4 weeks.

C. Chemotherapy
   i. As radiosensitizer – Chemotherapy with Cisplatin 40 mg/m2 or Carboplatin AUC 2 - 3 was given once a week during the course of PEBRT.
   ii. As active chemotherapy – Chemotherapy with Cisplatin 50 mg/m2 – Paclitaxel 135 mg/m2 every 3 weeks was given to patients with stable disease until patients had adequate response for brachytherapy. Cisplatin was replaced with Carboplatin AUC 5 - 6 when patient had azotemia during treatment.
   iii. Second Line Chemotherapy – Chemotherapy given to patients with persistent disease after a maximum of 6 cycles of active chemotherapy

D. Complete Radiation Therapy (CRT) – PEBRT followed by brachytherapy with or without weekly chemotherapy

2. Treatment Outcomes
   A. Adequate Response – Response to treatment of patients whose tumor characteristics were assessed to be suitable for brachytherapy after PEBRT with weekly chemotherapy
   B. Stable Disease – Inadequate response to treatment of patients whose tumor characteristics did not reach the requirements for brachytherapy, such as allowable tumor size (< 4 cm) or no parametrial involvement, either after PEBRT with weekly chemotherapy, or after maximum of 6 cycles of active chemotherapy
   C. Progressive Disease – Response to treatment of patients whose tumor characteristics achieved a tumor size allowable for brachytherapy after PEBRT with weekly chemotherapy but increased again in size after a certain period prior to having brachytherapy. This group of patients included those who initially had adequate response to PEBRT with chemotherapy but were not able to undergo brachytherapy right after for different reasons such as other medical conditions prohibiting the procedure, those who were lost to follow up or those who opted not to be treated and came back for follow up when brachytherapy was not possible anymore.
   D. No Evidence of Disease – Response to treatment of patients who had complete remission of cervical mass after treatment
   E. Recurrent Disease – Local or distant recurrence of disease after more than 3 months of having no evidence of disease. Local recurrence will be classified as those occurring in the cervix, pelvis or vagina. Distant recurrence, on the other hand, will be those found beyond the pelvis such as bones, liver, lung, inguinal region, central nervous system or other distant sites.

3. Outcomes of the Study
   A. Over-all Survival – Defined as the time in months from the date of histopathologic diagnosis until the date of death from any cause. Survivors were censored from the date of last contact.
   B. Recurrence Free Survival – Defined as the time in months from the last treatment to disease recurrence (for patients who underwent brachytherapy) or disease progression (for patients who did not undergo brachytherapy).

Study Subjects

A. Inclusion Criteria:

This study included all stage IIB – IVA cervical cancer patients confirmed by pathology and clinical examination who were diagnosed from January 2002 – December 2017 without any history of previous treatment for cervical cancer and who were treated with PEBRT with weekly chemotherapy with or without brachytherapy.

B. Exclusion Criteria:

Cervical cancer patients with early stage disease who had surgery as treatment and those who were detected to have para-aortic lymph node whether on treatment planning or any radiological examination prior to radiation who underwent Extended Field Radiation instead of PEBRT were not included in the study. Patients with other simultaneous malignancy, incomplete PEBRT or missing data or medical records were also excluded.

Data Collection

The data were collected from the Medical Records Section – Out Patient Department.

Patients were classified based on their treatment response:

Response 1 – Patients with adequate response to PEBRT with weekly chemotherapy who underwent brachytherapy

Response 2 – Patients with stable disease after PEBRT with weekly chemotherapy who were given active chemotherapy then underwent brachytherapy

Response 3 – Patients with stable disease after PEBRT with weekly chemotherapy who were given active chemotherapy but were not able to have brachytherapy

Response 4 – Patients with adequate response to PEBRT with weekly chemotherapy who were not able to undergo brachytherapy

Follow up

After complete radiotherapy with weekly radiosensitizer, patients were followed up 2 weeks after brachytherapy then every month for 3 months then at 3- month intervals for the first two years, at six month intervals for 3 additional years, and yearly thereafter. Standard surveillance included physical and pelvic examination and Papanicolau test with additional imaging studies and directed biopsies as indicated. For patients given active chemotherapy, follow-up while ongoing treatment was done 2 weeks after each chemotherapy session. All recurrent and progressive diseases were histologically and/or radiographically confirmed.

RESULTS

All analyses were done using the Statistical Package for the Social Sciences (SPSS Version 21). Numerical summaries included mean and their standard deviations and percentages. Univariate analysis was done using independent T-test for continuous data and Chi-Square for categorical responses. Regression analysis was used to determine treatment factors correlated to adequate response for brachytherapy. Odd ratios, with their 95% confidence intervals and p-values less than 0.05 were considered significantly associated with brachytherapy. The Kaplan Meier plots were constructed, and each category of response were compared using the log-ranks test. The mean and median OS and RFS time were determined for each response category. All tests of significance with p-values less than 0.05 were considered significant.

A total of 557 cases of LACC from January 2002 - December 2017 were included in this review. A total of 429 (77%) had adequate response after PEBRT and weekly chemotherapy and were assessed to be suitable for brachytherapy. Among these, 342 or 61.4% of the whole population underwent brachytherapy, while 87 (15.6%) did not undergo such treatment.

A total of 128 (23%) were classified to have stable disease after PEBRT with weekly chemotherapy and were evaluated not to be suitable for brachytherapy. They were offered with active chemotherapy instead. In this group, only 8 patients or 1.4% of the whole population had brachytherapy after receiving 2 to 6 cycles of active chemotherapy while 120 patients (21.5%) did not have the procedure (Figure 1).

A total of 350 (62.8%) cases of LACC had completed PEBRT plus weekly chemotherapy and underwent brachytherapy while 207 (37.2%) did not receive brachytherapy at all. Table 1 showed the profile of patients between the two groups.

Over-all Survival Analysis

The cumulative probability of the five-year OS between patients who had brachytherapy (Response 1 and 2) versus those who did not have brachytherapy (Response 3 and 4) was compared (Figure 2). The mean survival time of the first group was 34.9 versus 14.2 months for the second group.

The two survival curves significantly differed, with a statistically longer duration of survival among those who underwent brachytherapy (p=0.001).

Over-all Survival Time

Table 2 showed the mean and median survival time for each response category. Figure 3 showed the survival curves of all the response categories. Pairwise comparisons revealed that mean OS time was significantly longer in Response 1 versus Response 3 (p=0.032); Response 1 versus 4 (p=0.001); Response 2 versus 3 (p=0.003) and Response 2 versus 4 (p=0.011). The mean OS times were not statistically significant between Response 1 and Response 2 and between Response 3 and Response 4.

Recurrence Free Survival Analysis

The cumulative probability of the five-year RFS between patients who had brachytherapy (Response 1 and 2) versus those who did not have brachytherapy (Response 3 and 4) was compared (Figure 4). The mean RFS time of the first group was 42.3 versus 27.7 months for the second group.

The two survival curves significantly differed, with a statistically longer duration of RFS among those who underwent brachytherapy (p=0.038).

Recurrence Free Survival Time

Table 3 showed the mean and median survival time for each response category. Figure 5 showed the RFS curves of the all response categories. Pairwise comparisons revealed that mean RFS time was significantly longer in Response 1 versus Response 4 (p=0.011); Response 2 versus Response 4 (p=0.002) and Response 3 versus Response 4 (p=0.023). The mean RFS times were not statistically significant between Response 1 and Response 2, between Response 1 and 3 and between Response 2 and Response 3.

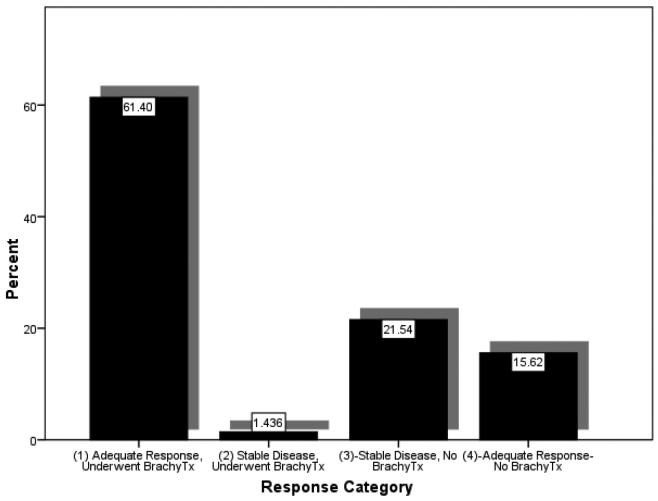

Figure 1. Response Classification of LACC with PEBRT and Weekly Chemotherapy from January 2002 to December 2017

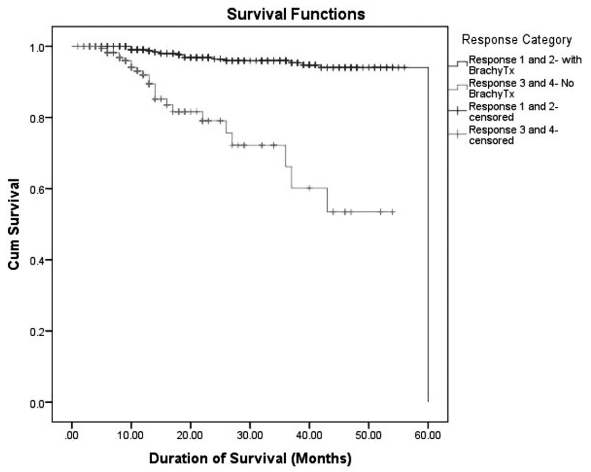

Figure 2. Kaplan Meier Overall Survival Plot for Cases of LACC with and without Brachytherapy (Response 1 & 2 versus Response 3 & 4) from January 2002 to December 2017

Table-1 Comparative Profile of LACC after PEBRT and Weekly Chemotherapy with and without Brachytherapy from January 2002 to December 2017

Characteristic	After PEBRT and Weekly Therapy		
	Response 1 & 2 with Brachytherapy	Response 3 & 4 without Brachytherapy	p-value
Total Patients (%)	350 (62.8)	207 (37.2)	
Mean age (SD)	50.9 (9.8)	48 (10.5)	0.001*
Stage II III IV	 101 (28.9) 249 (71.1) 0	 36 (17.4) 168 (81.2) 3 (1.4)	0.001**
Tumor size at start (%) < 5 cm ≥ 5 cm	 124 (35.4) 226 (64.6)	 38 (18.4) 169 (81.6)	0.001**
Tumor size at mid (%) < 50% ≥ 50%	 128 (36.6) 222 (63.4)	 47 (22.7) 160 (77.3)	0.001**
Histology (%) Squamous cell Adenocarcinoma Adenosquamous	 266 (76) 74 (21) 10 (2.9)	 143 (69.1) 53 (25.6) 11 (5.3)	0.13**
Chemotherapy None 1-3 >3	 5 (1.4) 33 (9.4) 312 (89.1)	 15 (7.2) 41 (19.8) 151 (72.9)	0.001**
Duration of PEBRT ≤ 45 days > 45 days	 123 (35.1) 227 (64.9)	 46 (22.2) 161 (77.8)	0.002**
Frequency of Anemia 0 1 2 3	 219 (62.6) 93 (26.6) 35 (10) 3 (0.9)	 88 (42.5) 68 (32.9) 44 (21.3) 7 (3.4)	0.001**
Parametrial boost None Present	 55 (15.7) 295 (84.3)	 18 (8.7) 189 (91.3)	0.019**

Table-2 Mean and Median Survival Time of LACC after PEBRT and Weekly Chemotherapy from January 2002 to December 2017

Mean[a]					Median			
RESPONSE	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Response 1	35.964	1.064	33.879	38.050	36.000	1.792	32.487	39.513
Response 2	34.000	7.326	19.642	48.358	38.000	16.398	5.860	70.140
Response 3	14.285	1.270	11.796	16.773	10.000	0.809	8.414	11.586
Response 4	14.307	1.309	11.742	16.872	9.000	1.159	6.728	11.272
Overall	28.352	0.880	26.627	30.077	23.000	1.571	19.922	26.078
a. Estimation is limited to the largest survival time if it is censored.								

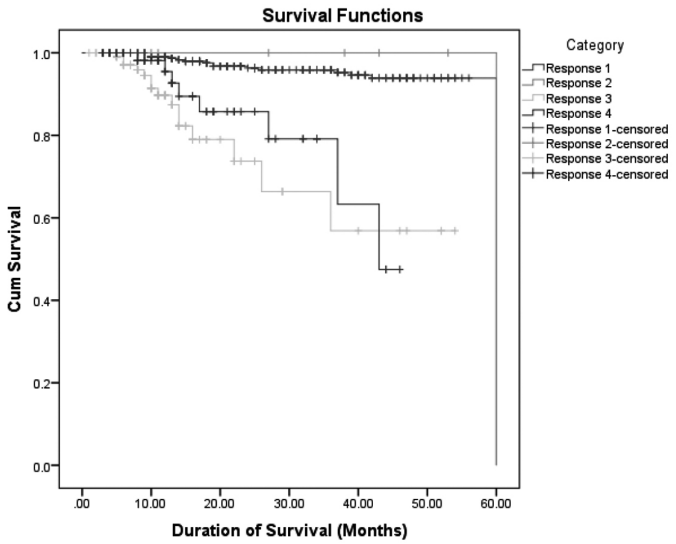

Figure 3. Kaplan Meier Overall Survival Plot for Cases of LACC with and without Brachytherapy and with or without Active Chemotherapy (Response 1 versus 2 versus 3 versus 4) from January 2002 to December 2017

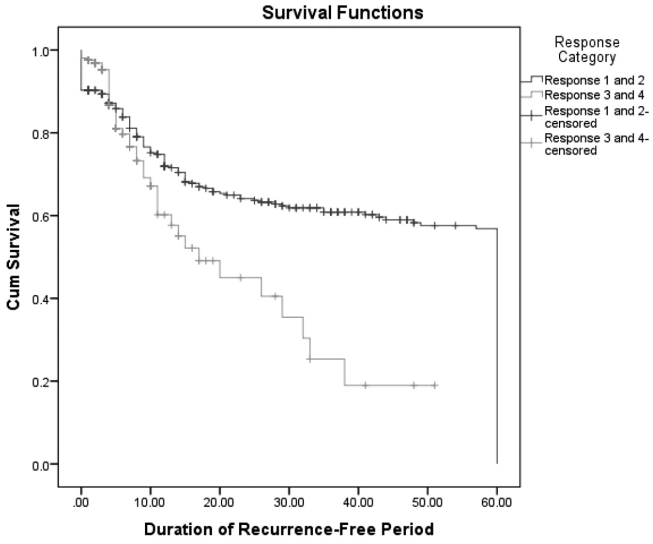

Figure 4. Five-Year Recurrence-Free Survival Plot for Cases of LACC with and without Brachytherapy (Response 1 & 2 versus Response 3 & 4) from January 2002 to December 2017

Table 3 Mean and Median Recurrence-Free Survival Time of LACC after PEBRT and Weekly Chemotherapy from January 2002 to December 2017

Mean[a]					Median			
RESPONSE	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Response 1	39.61	1.485	36.701	42.524	60.000	.000	22.7	27.5
Response 2	45.00	10.60	24.211	65.789	60.000	.000	--	--
Response 3	42.48	3.452	35.722	49.254	--	--	--	--
Response 4	13.11	1.788	9.605	16.614	9.000	1.306	6.4	11.56
Overall	38.2	1.3	35.640	40.865	60.000	.000	--	--
a. Estimation is limited to the largest survival time if it is censored. Blanks indicate non-estimable values								

Treatment Factors Correlated with Adequate Response for Brachytherapy

Among the treatment factors analyzed, the study showed that patients with >50% decrease in the original tumor size at the middle part of PEBRT (OR: 1.83, 95% CI: 1.2-2.8, p=0.005) and those who received more than 3 cycles of chemotherapy (OR: 2.6, 95% CI: 1.79-3.9, p=0.001) had higher odds for having adequate response for brachytherapy after PEBRT. Other factors such as histology type of non squamous cell carcinoma, initial tumor size of > 5 cm, completion of PEBRT for more than 45 days and having 2 or more episodes of anemia during PEBRT were found to have lower odds of leading to brachytherapy (Table 4).

Patients with Stable Disease after PEBRT with Weekly Radiosensitizer (Response 2 and 3)

There were 128 patients initially deemed as not candidates for brachytherapy after pelvic radiation. Table-5 showed the profile of patients who had stable disease treated with or without brachytherapy. Significant differences between the two groups were noted in terms of age, stage, tumor size at start and middle part of treatment, histology, and number of active chemotherapy and second line chemotherapy received (all p-values <0.05). Only eight patients (6.6%) were able to have brachytherapy after 2 – 6 cycles of active chemotherapy. Sixty patients (46.8%) among this group had no treatment at the initial diagnosis of stable disease after PEBRT. Some chose not to have treatment anymore, were lost to follow up or eventually succumb to the disease. The other sixty patients (46.5%) opted to receive active chemotherapy. Majority continued to have stable disease or had progressive disease during active chemotherapy and were offered to receive second line of chemotherapy.

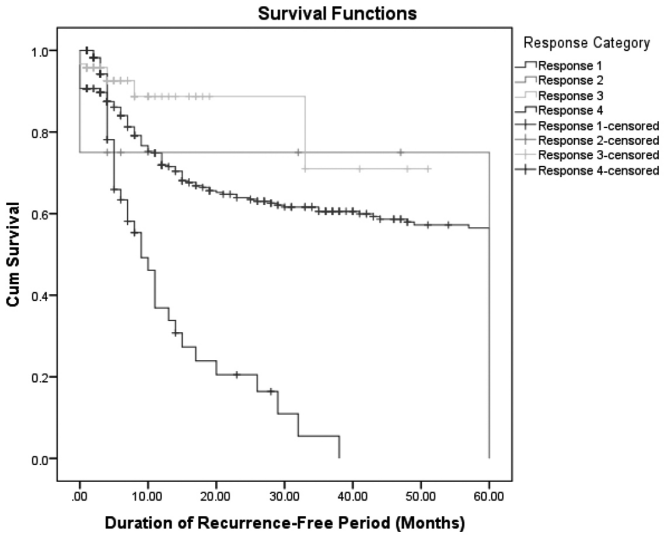

Figure 5. Kaplan Meier Recurrence-Free Survival Plot for Cases of LACC with and without Brachytherapy and with or without Active Chemotherapy (Response 1 versus 2 versus 3 versus 4) from January 2002 to December 2017

DISCUSSION

The OS and RFS were both significantly higher for patients who had brachytherapy compared to those who have not undergone the procedure. These results were compatible with other foreign studies implicating that the utilization of brachytherapy compared to using PEBRT alone is associated with better treatment and survival outcomes.[3-7]

Treatment Factors Correlated with Adequate Response for Brachytherapy

In the management of LACC, several factors affecting tumor response to treatment and survival were already well studied and documented. This study highlighted the factors as defined in the local setting that may affect treatment response as early as during pelvic radiation which shall be taken into account so that brachytherapy may be done to all patients as much as possible.

The results revealed that the initial tumor size is an important predictor of response to treatment. It showed that the bigger the initial tumor size (> 5 cm), the less likely it is to have adequate response for brachytherapy. However, patients whose tumors decreased in > 50% of its

Table 4 Regression Analysis of Treatment Factors during PEBRT of LACC from January 2002 to December 2017 Correlated with Adequate Response for Brachytherapy

Factor	OR	95% CI	p-value
Age	1.06	0.72-1.57	0.74
Stage	0.66	0.41-1.05	0.08
Non squamous histology	0.65	0.46 – 0.92	0.016*
≥ 5 cm Initial tumor size	0.41	0.26- 0.65	0.001*
≥ 50% Decrease in Tumor size at the middle of PEBRT	1.83	1.2-2.8	0.005*
> 3 Cycles of chemotherapy	2.66	1.79-3.9	0.001*
> 45 days of PEBRT	0.63	0.41-0.97	0.04*
≥ 2 episodes of anemia	0.67	0.52-0.85	0.001*

Table 5 Comparative Profile of LACC after PEBRT and Weekly Chemotherapy Categorized as Stable Disease, with (Response 2) and without Brachytherapy (Response 3) from January 2002 to December 2017

	After PEBRT and Weekly Chemotherapy		
	Response 2	**Response 3**	**p-value**
Mean Age (SD)	48.7	46.2	0.001
Stage			0.028
II	2 (25)	20 (16.7)	
III	6 (75)	98 (81.7)	
IV	0	2 (1.7)	
Initial tumor size			0.001
<5 cm	2 (25)	16 (13.3)	
≥5 cm	6 (75)	104 (86.7)	
Decrease in size at middle part of PEBRT			0.001
<50%	1 (12.5)	19 (15.8)	
≥50%	7 (87.5)	101 (84.2)	
Histology			0.015
SCCA	4 (50)	75 (62.5)	
Adenocarcinoma	4 (50)	36 (30)	
Adenosquamous	0	9 (7.5)	
Active chemotherapy			0.001
0	--	60 (50)	
1	--	4 (3.3)	
2	2 (25)	19 (15.8)	
3	3 (37.5)	15 (12.5)	
4	--	4 (3.3)	
5	--	10 (8.3)	
6	3 (37.5)	8 (6.7)	
Second Line Chemotherapy			0.001
No	8 (100)	67 (55.8)	
Yes	0	15 (12.5)	
Lost to ff up	0	38 (31.7)	

original size at the middle part of PEBRT were found to be 1.83 times more likely to have brachytherapy compared to those who had < 50% decrease in tumor size. Hence, accurate internal examination during the first consult followed by regular internal examination during treatment cannot be underestimated. Other treatment options may be discussed with the radiation oncologists such as possibly adjusting the radiation doses to those patients who do not reach a decrease in tumor size of > 50% at the middle part of treatment may be beneficial. Further studies with the use of different radiosensitizers other than the usually administered platinum-based chemotherapy drugs to those with tumors measuring > 5 cm may be useful.

Moreover, the benefits of giving chemotherapy as radiosensitizer has already been well documented.[3,4,8] This was also in agreement with the results of the current study revealing that patients who had more than 3 cycles of weekly chemotherapy as radiosensitizer were 2.66 times more likely to be good candidates for brachytherapy after PEBRT compared to those patients who only had 3 or less cycles of radiosensitizers. Indeed, patients during PEBRT shall be encouraged not to miss any cycle of their weekly chemotherapy to be able to have tumor regression and characteristics qualified for brachytherapy.

Likewise, it is a well known fact that a shorter treatment time significantly improves survival and treatment outcomes.[5,7] Researches showed varied optimal treatment duration for patients undergoing CRT. Petereit et al concluded that each additional day of treatment delay beyond 55 days was associated with a 0.7% loss of pelvic control and a 0.6% reduction in survival.[10] However, there was no mention with regards to an expected number of days of pelvic radiation alone to make the patient qualify for brachytherapy. If with no treatment delays, a patient is expected to finish pelvic radiation concurrent with six cycles of chemotherapy in 45 days or one and a half months. In this review, it was shown that PEBRT done in > 45 days was significantly less correlated to having adequate response prior to brachytherapy. There may be unforeseen circumstances such as damages or unavailability of

machines, anemia, or other conditions when patients skip their treatment sessions. Indeed, every effort shall be made to finish CRT in 55 days. Some institutions use "sandwich" method wherein brachytherapy is being started already prior to the completion of PEBRT. This may also be considered to shorten over-all treatment time, thus improving treatment and survival outcomes. Again, accurate internal examination followed by regular internal examination during treatment cannot be underestimated. This may help clinicians to come up with proper timing and decision when to initiate brachytherapy even during the last few days of PEBRT.

Studies have conflicting results with regards to treatment and survival outcomes between squamous and non-squamous cell carcinoma.[4,11-13] Katanyoo et al, in their study comparing treatment outcomes between squamous cell carcinoma and adenocarcinoma in LACC, concluded that the former histology type had poorer response rate from treatment and also had longer time to achieve complete response than squamous cell type. However, these effects were not determinants of survival outcomes. Chen et al, on the other hand, found this histology type to be a significant prognostic factor with worse OS, disease free survival and local failure-free survival as compared to squamous cell carcinoma. Another study has stated that adeno- and adenosquamous carcinoma of the cervix are associated with similar progression free and overall survival compared to squamous cell carcinomas when treated with cisplatin based chemoradiation.[13] On the contrary, this analysis showed that patients with non-squamous cell carcinoma of the cervix were less likely to have adequate response for brachytherapy. Different treatment options such as having another radiosensitizer or administering first active chemotherapy prior to PEBRT may be more beneficial to non-squamous histology type than its current standard of care. However, this should be further investigated in future prospective studies.

It is also well understood that lower radiosensitivity is expected in patients with anemia and poorly oxygenated tumors, implicating the association between hemoglobin levels before and during treatment and tumor response.[4,6] In addition to this, anemia may lead to lesser cycles of chemotherapy and further treatment delays, extending the total treatment time. However, significant hemoglobin levels were defined differently in researches. Chen et al used a cut off value of 11 g/dL and stated that pretreatment lower hemoglobin level than this was associated with poorer local control. In this current study, anemia was defined as hemoglobin level of < 10 g/dL and patients who had 2 or more episodes of anemia during their pelvic radiation were found to be less likely to have adequate response for brachytherapy.

Patients with Stable Disease given Active Chemotherapy who eventually had Brachytherapy (Response 2)

This study revealed that OS of those patients who were given active chemotherapy until the time they became suitable for brachytherapy (Response 2) was comparable to those patients who had brachytherapy right after pelvic radiation (Response 1) (p=0.32). However, it was significantly different from those who were not able to receive brachytherapy with or without active chemotherapy (Response 3 and 4) (p=0.003 and p=0.011), respectively. In terms of RFS, these patients who were given active chemotherapy and eventually was able to have brachytherapy had comparable RFS to the first and third response groups. But it was found to be significantly different from those patients who did not have any other treatment other that pelvic radiation and concurrent chemotherapy (p=0.02). Thus, for stable disease after pelvic radiation with weekly chemotherapy, all efforts shall be made to reach the goal of administering brachytherapy to these patients.

Patients with Stable Disease given Active Chemotherapy who did not have Brachytherapy (Response 3)

The data showed that the RFS of those who were given active chemotherapy but did not have brachytherapy (Response 3) was not significantly different from those who had brachytherapy with or without active chemotherapy (Response 2 and 1). However, the group's OS was still comparable to those who did not have brachytherapy at all (Response 4) (p=0.44).

These data showed that active chemotherapy may offer some benefit in terms of delaying tumor recurrence or progression, which is expected since patient is still receiving some form of treatment against malignant cells. However, this benefit did not translate to survival impact if the patient was not able to have brachytherapy at all. Hence again, active chemotherapy may still be offered to those patients who are initially not good candidates for brachytherapy after pelvic radiation concurrent with chemotherapy with the goal of still administering brachytherapy as soon as possible. If other advanced technique of radiation such as IGBT, interstitial brachytherapy or IMRT are not readily available, active chemotherapy may be an option for this group of patients with stable disease. Option of referrals to other institutions with such radiation facilities shall also be considered and be offered to the patients.

Patients with Adequate Response after PEBRT with Weekly Radiosensitizer but did not undergo Brachytherapy (Response 4)

Figure 1 showed that majority of the patients who underwent pelvic radiation with concurrent weekly chemotherapy had adequate response to this

treatment and were then considered good candidates for brachytherapy (77%). A small percentage of this population (15.6%) were not able to have brachytherapy. Most of them were lost to follow up, some returning only with already signs and symptoms of tumor progression, making them not capable of having brachytherapy anymore. These patients need to be counselled very well since the results showed that the tumor is more likely to progress again after 13 months of not having the treatment. This finding should also be noted in scheduling of patients for brachytherapy, indicating that treatment delay should not exceed 13 months. If with long queue of patients, referrals to other institutions with radiation facilities shall again be considered and be offered to the patients.

Meanwhile, OS for this group of patients was computed to be at 14.2 months, which, as previously stated, was comparable to those patients who had stable disease and were not able to have brachytherapy despite active chemotherapy (p=0.44). This results strengthen the impact of brachytherapy on survival outcomes.

SUMMARY AND CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

Brachytherapy provides lesser tumor recurrence and leads to improved survival outcome for patients with LACC. It is indeed an essential component in the treatment of cervical cancer patients. Knowing the different factors that are associated with having adequate response for brachytherapy, all efforts should be made to be able to include this technique in each patient's treatment plan.

For patients who cannot have brachytherapy right after pelvic radiation with concurrent chemotherapy, active chemotherapy may be a good treatment option for tumor control. However, this benefit did not translate to survival impact if the patient was not able to have brachytherapy at all. To date, no other treatment options were proven to replace nor even equate the treatment and survival outcome benefits of brachytherapy in the management of cervical cancer. And until there is lack of data that may provide better options to patients not able to undergo the procedure, brachytherapy remains to be a necessity in the treatment of LACC and it shall never be just an option.

This was a retrospective study and was limited by the availability and accuracy of the records retrieved at the Medical Records. The population was derived from a single tertiary hospital and data may not be the same with other population. The heterogeneity between those with and without brachytherapy was expected since the variety of factors used were also treatment variables that might have affected the treatment response of patients. Finally, the low number of patients on some subgroups may be considered as another limitation in this study, just like in any other retrospective analysis wherein manipulation of the subject population is not possible.

Whether patients who are not candidates for brachytherapy will benefit to more advanced type of radiation boost or other form of treatment such as active chemotherapy, was not included in the scope of this study. Future prospective studies with similar objectives may be done to improve the quality of the results of this current analysis. This may also lead to further studies that may improve the current management on LACC. ■

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