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Neoadjuvant radiotherapy followed by hysterectomy in locally advanced endometrial cancer: Outcomes from a tertiary government hospital in the Philippines

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A B S T R A C T

Objective: Managing endometrial cancer with suspected or gross cervical involvement lacks a standard approach. This study evaluated outcomes in patients with cervical and/or parametrial involvement treated with neoadjuvant radiation followed by hysterectomy.

Methods: Fourteen patients from 2007 to 2022 with locally advanced endometrial cancer and cervical and/or parametrial involvement were retrospectively analyzed. They received neoadjuvant external beam radiotherapy (45–50.4 Gy in 25–30 fractions) and high-dose rate brachytherapy (5.5–7.0 Gy per fraction in 3–4 fractions), followed by extrafascial hysterectomy. Clinical data, pathologic response, and survival outcomes were assessed, along with factors associated with pathologic response.

Results: Most patients (86%) had stage III disease with cervical extension, 93% had parametrial involvement, and 14% had nodal involvement. Chemotherapy was given to 86% either concurrently or adjuvantly. Post-surgery, 86% had no pathologic cervical involvement, and 93% had negative surgical margins. Pathologic complete response was seen in 43%. Locoregional recurrence occurred in 14%. Median follow-up was 30 months, with recurrence-free survival and overall survival rates of 86% and 100%, respectively. Lower grade tumors significantly correlated with pathologic complete response ($\Phi = 0.72$, $p = 0.026$). No significant correlation was found between pathologic complete response and other factors. No late grade 3–4 toxicities were reported.

Conclusion: Neoadjuvant radiation followed by hysterectomy, with or without chemotherapy, is a viable strategy for managing endometrial cancer with cervical and/or parametrial involvement. This approach enhances resectability, yielding high rates of pathologic complete response and negative resection margins, showing promise for this challenging patient group.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States (Siegel et al., 2019 Jan) and the 7th leading site among women in the Philippines. (Laudico et al., 2010) The majority of women, around 85% of the time (SGO Clinical Practice Endometrial Cancer Working Group et al., 2014 Aug), present with uterine confined disease managed with primary surgical resection. The standard of care for endometrial cancer includes surgical staging with total hysterectomy, bilateral salpingo-oophorectomy and lymph node assessment with adjuvant therapy including radiation and chemotherapy depending on risk factors found on pathology. (Jang and Lee, 2019 Jul 20).

Around 10–15% of cases, patients with endometrial cancer can have extensions to the cervix and parametrium involvement which can complicate upfront surgical intervention. (Creasman et al., 2004 Dec; Ahmad et al., 1989 Mar 1) Radical hysterectomy has been traditionally used for these subsets of patients but have resulted in surgical complications given the patient population's advanced age and significant comorbidities. (Gilbaz et al., 2013) Currently, there is a lack of randomized data to guide how these cases should be managed with a standard of care approach. The National Comprehensive Cancer Network Clinical Practice Guidelines 2023(NCCN, 2022) and Society of Gynecologic Oncologists of the Philippines Treatment Guidelines 2019 (Clinical Practice Guidelines, 2019) states that hysterectomy is preferred and the use of neoadjuvant external beam radiotherapy and brachytherapy followed by hysterectomy (Category 2B) is an additional treatment approach based on several reported series. (Secord et al., 2009 Sep; Reisinger et al., 1992 May).

Despite the reported favorable outcomes of upfront radiation based on several retrospective studies, (Conway et al., 2019 Oct; Vargo et al., 2014 Nov; Iheagwara et al., 2019 Jul; Gannavarapu et al., 2020 Mar; Horne et al., 2015) there has been a lack of local data in the Philippines

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with the use of neoadjuvant radiation in unresectable endometrial cancer. This study aims to report on the outcomes of locally advanced endometrial cancer with cervical and parametrial involvement managed with neoadjuvant external beam radiotherapy and brachytherapy followed by hysterectomy in a tertiary government hospital in the Philippines.

2. Materials and methods

A. Study Design

This study is a retrospective analysis of adult patients with locally advanced endometrial cancer with cervical and/or parametrial involvement treated with neoadjuvant radiotherapy followed by hysterectomy at Jose R. Reyes Memorial Medical Center (JRRMMC) from 2007 to 2022. After obtaining approval from the Institutional Review Board of JRRMMC with waiver of informed consent, all adult patients from January 2007 to May 2022 with histologically proven endometrial cancer with clinical involvement of the cervix and/or parametrium at diagnosis and treated with neoadjuvant external beam radiotherapy followed by high dose rate brachytherapy and subsequently underwent hysterectomy with or without concurrent or adjuvant chemotherapy were included. Patients with a history of prior pelvic irradiation, distant metastasis at the time of diagnosis and were deemed inoperable because of medical comorbidities were excluded from the study.

B. Treatment

All patients with biopsy proven endometrial cancer included were assessed clinically to determine extent of disease. Pre-treatment evaluations included whole abdominal ultrasound (85.7%), computed tomography of the abdomen and pelvis (35.7%) and chest radiography (100.0%). Neoadjuvant radiotherapy consisted of external beam radiotherapy delivered via Cobalt-60 teletherapy machine with direct planning or Linear Accelerator planned with computed tomography (CT) to a dose of 45–50.4 Gy given in 25–30 fractions with or without parametrial boost (10–10.8 Gy in 5–6 fractions) and/or midline shielding after 39.6 or 40 Gy. Patients who were simulated using CT had clinical target volumes which included the entire gross tumor, cervix, uterus, ovaries, parametria, proximal ½ of vagina (entire vagina if with vaginal involvement) and pelvic nodes starting from the bifurcation of the common iliac vessels to include bilateral common iliac, external iliac, internal iliac, presacral, obturator lymph node regions. Extended field radiation which includes the treatment of the entire *para*-aortic chain was done for *para*-aortic node positive patients. This was followed by high-dose rate brachytherapy prescribed to Point A based on orthogonal radiographs to a dose of 5.5–7.0 Gy per fraction given in 3 to 4 fractions depending on the discretion of the treating radiation oncologist. Total doses were combined and adjusted to equivalent 2 Gy doses (EQD2) using an assumed α/β ratio of 10 for tumors and 3 for normal tissues. Surgery performed included an abdominal extrafascial hysterectomy and salpingo-oophorectomy. Nodal dissection was done for patients who had suspicious intraoperative node on evaluation at the discretion of the operating surgeon while concurrent or adjuvant chemotherapy were prescribed based on the discretion of the gynecologic oncology service.

C. Data Collection

Patient demographics and tumor characteristics including age at diagnosis, histologic subtype, tumor grade, initial clinical stage and pretreatment evaluations were documented. Data of the timing of biopsy, radiation, surgery, and chemotherapy were also recorded. Radiation treatment data which include the type of external beam treatment modality, target volumes, brachytherapy planning method, dose fractionation of external beam radiotherapy and brachytherapy and cumulative equivalent dose were noted. The extent of hysterectomy and surgical procedure as well as the chemotherapeutic regimens, if given, were documented. Pathologic response was evaluated based on the surgical pathology reports after hysterectomy and other endpoints including overall survival and recurrence were reviewed from follow up data.

D. Assessment Instruments

Pathologic responses were assessed using the final surgical pathology report after hysterectomy. Surgical margins, residual myometrial involvement, presence of lymphovascular space invasion, tumor grade, and nodal involvement were evaluated. Overall pathologic response was classified as complete response, microscopic residual disease or incomplete response. Patients after treatment were followed up periodically with clinical examination and/or radiologic imaging and workups to determine recurrences. Tumor control and survival were evaluated based on the follow up data available calculated from the date of biopsy to the date of the event or last follow-up/death. Toxicities from radiation were graded using the Radiation Therapy Oncology group (RTOG) radiation morbidity grading system.

E. Data Analysis

Statistical analyses were conducted using STATA MP Parallel Edition Statistical Software, Version 18, College Station, TX: StataCorp LP. A p-value ≤ 0.05 was considered statistically significant. Descriptive statistics involved mean and standard deviation for normally-distributed, continuous data; median and interquartile range (IQR) for ordinal and non-normally-distributed, continuous data; and, frequency and proportions for categorical data. Data normality was evaluated using Shapiro-Wilk's Test. The associations of pathologic complete response with recurrence-free survival, overall survival, and the different factors (age at diagnosis, clinical stage, nodal involvement, tumor size, grade, histology, EQD2 equivalent dose, radiation technique, and time between surgery and radiotherapy) were conducted using phi (Φ) coefficient. Phi coefficient is a statistical test of the association between two nominal data with values ranging from –1.00 to 1.00. A phi coefficient of ≥ 0.20 is considered a weak correlation, while coefficient value of ≥ 60 is classified as a strong correlation, respectively. In addition, Cox proportional-hazards regression was employed to determine the association, in terms of hazards ratio, between pathologic complete response with recurrence-free and overall survival. Comparison of survival estimates between those with and without pathologic complete response was performed using the log-rank test. Median splitting approach was conducted to categorize the age at diagnosis, tumor size, EQD2 equivalent dose, and time between surgery and radiotherapy.

3. Results

A total of fourteen patients were included in the analysis. Table 1 presents the demographic and tumor characteristics of the patients. Results showed that the mean age of the participants was 53.3 years old (SD=6.7). In terms of stage, results showed that the majority had stage III disease (85.7%). All patients had cervical involvement with two involving the upper vagina on examination (14.3%). Thirteen patients had parametrial involvement (92.9%). Two patients (14.3%) had pelvic nodal involvement and 1 patient had involvement of the *para*-aortic region, specifically a pre-caval node. Thirteen of the fourteen (92.9%) patients had endometrial histology, while the average tumor size is 6.0 cm. All patients were evaluated with internal examination to determine clinical extent of the disease. Pre-treatment evaluation included ultrasonography of the whole abdomen which was done in 12 patients (85.7%) while 4 patients (28.6%) had computed tomography of the whole abdomen. All patients had chest radiographs as part of evaluation.

The radiotherapy characteristics of the patients are depicted in

Table 1
Baseline Patient Characteristics *(N=14)*.

Characteristics	Summary Statistic
Age (Years; $\bar{x}$, SD)	53.3 (6.7)
Stage (*n*, %)	
Stage I	0 (0.0%)
Stage II	2 (14.3%)
Stage III	12 (85.7%)
Stage IV	0 (0.0%)
Clinical Involvement	
Cervix	14 (100.0%)
Vaginal Involvement	
None	12 (85.7%)
Upper	2 (14.3%)
Mid	0 (0.0%)
Lower	0 (0.0%)
Parametrial Involvement	
None	1 (7.1%)
Involved	13 (92.9%)
Nodal Involvement (*n*, %)	
Pelvic Lymph Node	2 (14.3%)
Para-aortic Lymph Nodes (PALN)	1 (7.1%)
Histology	
Non-Endometrioid	1 (7.1%)
Endometrioid	13 (92.9%)
Tumor Size ($\bar{x}$, SD)	6.00 (1.2)

Note: Md = Median, IQR=Interquartile Range, $\bar{x}$= Mean, SD=Standard Deviation

Table 2. It can be noted that the most common technique of external beam radiotherapy (EBRT) was 2-D approach (64.3%) and 13 (92.9%) of patients were treated with a standard pelvic field radiation. Total external beam radiation dose ranges from 45-50 Gy treated in 1.8–2.0 Gy per fraction in 25 fractions. Three patients (21.4%) received parametrial boost of 10 Gy delivered in 5 fractions. In terms of brachytherapy, all patients were treated using a 2-D approach with the majority of them (92.9%) delivered via a Fletcher-Suit applicator. Most of the patients (71.4%) were prescribed 7 Gy per fraction to point A (point at 2 cm superior from the tandem flange and 2 cm lateral from the center of the tandem) given in three (35.7%) to four (64.3%) fractions. The median total prescription dose to the tumor was estimated to be at 79.40 Gy.

Table 2
Radiotherapy Technique (N=14).

Characteristics	Summary Statistic
External Beam Radiotherapy Technique (*n*, %)	
2-D	9 (64.3%)
3-D	5 (35.7%)
IMRT	0 (0.0%)
External Beam Radiotherapy Details (*n*, %)	
Pelvic field	14 (100.0%)
Extended field	1 (7.1%)
Dose per fraction (Md, IQR)	180 (180 – 200)
Parametrial Boost (f, %)	3 (21.4%)
Midline Shielding (f, %)	6 (42.9%)
Brachytherapy Technique (*n*, %)	
2-D	14 (100.0 %)
IGBT	0 (0.0%)
No. of brachytherapy fractions (*n*, %)	
3	5 (35.7%)
4	9 (64.3%)
Dose fractionation (*n*, %)	
5.5 x 3	1 (7.1%)
6.0 x 3	1 (7.1%)
6.0 x 4	2 (14.3%)
7.0 x 3	3 (21.4%)
7.0 x 4	7 (50%)
Brachytherapy Applicator (*n*, %)	
Fletcher-Suit	13 (92.9%)
Henschke	1 (7.1%)
Total Prescription Dose (Md, IQR)	
Overall	79.40 (69 – 81.42)

Note: Md = Median, IQR=Interquartile Range, $\bar{x}$= Mean, SD=Standard Deviation

In terms of surgical resection, all patients were managed with an abdominal extrafascial hysterectomy and bilateral salpingo-oophorectomy. Surgical resection was conducted at a median of 6.5 weeks following completion of radiation therapy. On review of the operative records, eight patients (57.1%) had pelvic nodal dissection while 5 (35.7%) patients had palpation only during the surgery. None of the patients underwent *para*-aortic lymph node dissection.

Among patients treated with systemic therapy, three patients (21.4%) received concurrent chemotherapy with radiation followed by adjuvant chemotherapy. Concurrent chemotherapy consisted of cisplatin and adjuvant chemotherapy consisted of carboplatin-paclitaxel given in five to six cycles. Eight patients (57.4%) received adjuvant chemotherapy only. Two patients did not receive systemic treatment while one received palliative chemotherapy after developing metastasis on follow up.

Table 3 illustrates the pathologic responses of the patients in the study. Thirteen patients had negative margins upon surgery while 1 patient had a positive margin. Six patients had no residual myometrial involvement, 5 (35.7%) had less than ½ residual myometrial involvement while 3 (21.4%) had more than ½ residual myometrial involvement. Only 1 patient had lymphovascular invasion on surgical pathology. In terms of grading, the majority of the patients were grade 1. The pathologic complete response rate was 42.9%.

The descriptive statistics of the response rates, recurrence rates, and overall and recurrence-free survival rates are presented in Table 4. It can be noted that 42.9% had pathologic complete response, while 57.1% had microscopic residual disease. In terms of recurrence rates, 2 patients (14.3%) had locoregional recurrence, with a median time of 20.3 months (IQR=18.57 to 22). Both recurrences were found in the vaginal cuff and confirmed with biopsy. One patient (7.1%) who recurred in the stump subsequently developed a distant metastasis which was detected on PET-CT and was treated with palliative chemotherapy. It can also be noted that all participants survived (100.0%) within a median follow-up period of 30.4 months (IQR=17.57 – 45.30). On the other hand, the

Table 3
Pathologic Response Results *(N=14)*.

Characteristics	Summary Statistic
Posttreatment pathologic cervical involvement (*n*, %)	2 (14.3%)
Surgical Margins (*n*, %)	
Positive Margins	1 (7.1%)
Close Margins	0 (0.0%)
Negative Margins	13 (92.9%)
Residual Myometrial Involvement (*n*, %)	
No Residual	6 (42.9%)
< ½ Residual	5 (35.7%)
> ½ Residual	3 (21.4%)
Lymphovascular Space Invasion (*n*, %)	1 (7.1%)
Pelvic Washing	
Negative	4 (28.6%)
Positive	0 (0.0%)
Not done	10 (71.4%)
FIGO Grade (*f*, %)	
Grade 1	6 (42.9%)
Grade 2	5 (35.7%)
Grade 3	3 (21.4%)
AJCC 8th edition yp Stage (*n*, %)	
ypT0	6 (42.9%)
ypT1a	4 (28.6%)
ypT1b	2 (14.3%)
ypT2	1 (7.1%)
ypT3b	1 (7.1%)
Overall Pathologic Response	
Pathologic Complete Response	6 (42.9%)
Microscopic Residual Disease	8 (57.1%)
No Response	0 (0.0%)

Note: Md = Median, IQR=Interquartile Range, $\bar{x}$= Mean, SD=Standard Deviation, yp = post-neoadjuvant.

Table 4
Outcomes and Survival Rates *(N=14)*.

	Frequency (%)	Median (IQR)	95% CI
Recurrence Rates			
Locoregional Recurrence	2 (14.3%)		3.1% to 46.5%
Interval from Biopsy to Locoregional Recurrence(months)		20.3 (18.57 – 22)	–
Distant Recurrence	1 (7.1%)		–
Interval from Biopsy to Distant Recurrence (months)		20.6 (–)	–
Overall Survival	14 (100.0%)		–
Interval from Biopsy to Survival Follow-up (months)		30.4 (17.57–45.30)	–
Recurrence-Free Survival	12 (85.7%)		53.5% to 96.9%

Table 5
Associations of Response Rates with Overall and Recurrence-Free Survival among the Participants (N=14).

Survival Rates	Pathologic Complete Response		Φ Coefficient	*p*-value
	No (n = 8)	Yes (n = 6)		(Two-Tailed)
Recurrence-Free Survival (*n*, %)			–0.47	0.078
With recurrence	0 (0.0%)	2 (33.3%)		
Without recurrence	8 (100.0%)	4 (66.7%)		
Overall Survival (*n*, %)			–	–
Expired	0 (0.0%)	0 (0.0%)		
Alive	8 (100.0%)	6 (100.0%)		

*Significant at 0.05.
†Significant at 0.01.

recurrence-free survival among the participants was 85.7%.

Table 5 illustrates the associations of survival rates with pathologic complete response. It can be noted that among those with recurrence-free survival, 66.7% had pathologic complete response. In addition, all participants who had survived had pathologic complete response (100.0%). Analysis indicated that recurrence-free survival and pathologic complete response had a negative, moderate correlation wherein higher recurrence-free survival trended towards incomplete pathologic complete response. Nevertheless, this association was not statistically significant ($\Phi = -0.47$, $p = 0.078$). Cox proportional-hazards regression analyses also showed a negative, yet non-statistically significant association (HR=0.55, $p = 0.383$). Analyses also showed that the median recurrence-free survival of those with pathologic complete response was 35.10 months (IQR=27.13 – 170.20), while those without pathologic complete response had a median recurrence-free survival of 28.6 months (IQR=13.30 – 45.30). Comparison of recurrence-free survival estimates according to pathologic complete response status was not statistically significant ($\chi^2 = 0.78$, $p = 0.376$). On the other hand, Cox proportional-hazards regression analyses also showed a negative, yet non-statistically significant association between pathologic complete response and overall survival (HR=0.80, $p = 0.706$). The median overall survival estimate of those with pathologic complete response was 28.57 months (IQR=13.30 – 45.30), while those without pathologic complete response had a median overall survival estimate of 27.13 months (IQR=25.23 – 41.13). The comparison of overall survival estimates between those with and without pathologic complete response status was also not statistically significant ($\chi^2 = 0.14$, $p = 0.706$).

The associations of pathologic complete response with the different clinical characteristics are depicted in Table 6. Results showed that among those with pathologic complete response, majority were $\geq$ 51 years old at the time of diagnosis (66.7%), were at clinical stage III (83.3%), did not have nodal involvement (83.3%), had tumor size $<$ 6.12 cm (66.7%), had grade I tumor (83.3%), had endometrioid tumors by histology (100.0%), received radiotherapy via 2-D approach (66.7%), and had a time interval between surgery and radiotherapy of $<$ 45.50 days (66.7%). Correlation analyses using phi coefficient indicated that age at diagnosis, clinical stage, nodal involvement, tumor size, histology, EQD2 equivalent dose, radiotherapy technique, and time between surgery and radiotherapy were not statistically associated or correlated ($p > 0.05$). However, it can be noted that the tumor grade was significantly associated with pathologic complete response ($\Phi = 0.72$, $p = 0.026$). This result denotes a very strong, positive association with tumor grade and pathologic complete response, those with pathologic complete response had lower tumor grades.

Most acute skin toxicities were grade 1, while the majority had grade 1 (28.6%) and grade 2 gastrointestinal (71.4%) and genito-urinary toxicities (35.7%). Grade 3 skin toxicity was the worst acute skin toxicity recorded, affecting 14.3% of the participants. In contrast, the worst acute gastrointestinal and genito-urinary toxicities were grade 2 (71.4%) and grade 1 (35.7%), respectively. For late toxicities, most participants had grade 1 skin (78.6%) and grade 1 gastrointestinal toxicities (57.1%). However, the worst late toxicities of the skin and gastrointestinal systems were grade 2, affecting 14.3% and 21.4%, respectively, of the participants. None of the participants developed late genito-urinary toxicities.

4. Discussion

In this retrospective study, we demonstrated that locally advanced endometrial cancer with extension to the cervix and parametrium treated with neoadjuvant external beam radiotherapy with HDR brachytherapy followed by hysterectomy had high pathologic response rates. Upfront radiation effectively improves resectability of the disease resulting in high rates of negative resection margins and complete pathologic responses in patients. Analyzing various clinical factors, pathologic complete response was significantly associated with tumor grade. However, there was no significant association between pathologic response and age at diagnosis, stage, nodal involvement, tumor size $>$ 6 cm, histology, EQD2 $>$ 79.40 Gy, radiotherapy technique, time between surgery and radiotherapy.

Women with locally advanced endometrial cancers presenting with extension to the cervix and parametrium is estimated to be 10–15% of all uterine cancers. (Creasman et al., 2004 Dec; Ahmad et al., 1989 Mar 1) The presence of these disease extensions poses a challenging treatment dilemma of either receiving radical hysterectomy followed by adjuvant therapy based on surgical pathology or neoadjuvant therapy followed by a less extensive surgery of extrafascial hysterectomy. (NCCN, 2022) Retrospective studies have suggested that radical hysterectomy provided better local control and survival than initial extrafascial hysterectomy. (Boente et al., 1993 Dec; Sartori et al., 2001) However, data

Table 6
Associations of Pathologic Complete Response with Different Clinical Characteristics (N=14).

Characteristics	Pathologic Complete Response		Φ Coefficient	*p*-value
	No (n = 8)	Yes (n = 6)		(Two-Tailed)
Age at Diagnosis			0.04	0.872
≤50 Years Old	3 (37.5%)	2 (33.3%)		
≥51 Years Old	5 (62.5%)	4 (66.7%)		
Clinical Stage (*n*, %)			–0.06	0.825
Stage II	1 (12.5%)	1 (16.7%)		
Stage III	7 (87.5%)	5 (83.3%)		
Nodal Involvement (*n*, %)			0.06	0.825
Without Nodal Involvement	7 (87.5%)	5 (83.3%)		
With Nodal Involvement	1 (12.5%)	1 (16.7%)		
Tumor Size (cm; $\bar{x}$, SD)			–0.29	0.280
<6.12 cm	3 (37.5%)	4 (66.7%)		
≥6.12 cm	5 (62.5%)	2 (33.3%)		
Grade (*n*, %)			0.72*	0.026
Grade I	1 (12.5%)	5 (83.3%)		
Grade II	4 (50.0%)	1 (16.7%)		
Grade III	3 (37.5%)	(0.0%)		
Histology (*n*, %)			0.24	0.369
Non-Endometrioid	1 (12.5%)	0 (0.0%)		
Endometrioid	7 (87.5%)	6 (100.0%)		
EQD2 Equivalent Dose (*n*, %)			0.00	1.000
<79.40	4 (50.0%)	3 (50.0%)		
≥79.40	4 (50.0%)	3 (50.0%)		
Radiotherapy Technique (*n*, %)			–0.04	0.872
2-D	5 (62.5%)	4 (66.7%)		
3-D	3 (37.5%)	2 (33.3%)		
Time between Surgery and Radiotherapy (*n*, %)			–0.29	0.280
<45.5 Days	3 (37.5%)	4 (66.7%)		
≥45.5 Days	5 (62.5%)	2 (33.3%)		

*Significant at 0.05.
†Significant at 0.01.

from Gilbaz et al reported that radical hysterectomy could result in more voiding dysfunction and possibly higher complication rates especially for endometrial cancer patients of advanced age with co-morbidities. (Gilbaz et al., 2013; Vargo et al., 2014 Nov).

Neoadjuvant radiation has been utilized in endometrial cancer extending to the cervix with parametrial invasion to improve outcomes. (Reisinger et al., 1992 May) Concerns about radiation increasing surgical morbidities because of fibrosis, compromised healing, and damage to normal tissue could be raised, however, retrospective data has shown decrease in complication rates from 2D planning to 3D planning. (Landgren et al., 1976 Jan; Mackillop and Stage, 1985; Conway et al., 2019 Oct) Advancements in radiation particularly image guidance, conformal treatment such as intensity modulated radiotherapy, and high-dose rate brachytherapy with 3D planning(Dankulchai et al., 2014 Jul) have improved target delineation and treatment delivery with abilities of escalating doses while limiting side effects. (Pötter et al., 2018 Feb) The delivery of upfront radiation can be given via pelvic external beam radiotherapy (EBRT) followed by brachytherapy. However, the doses are mainly dictated by institutional practices based on reported series (Conway et al., 2019 Oct; Vargo et al., 2014 Nov; Iheagwara et al., 2019 Jul; Gannavarapu et al., 2020 Mar).

Currently, there is no existing randomized trial data regarding the use of neoadjuvant radiation in the management of endometrial cancer. Despite the lack of randomized evidence to influence the optimal treatment approach, for medically operable locally advanced endometrial cancer deemed unresectable because of cervical, parametrial and vaginal involvement, the National Comprehensive Cancer Network Clinical Practice Guidelines 2023(NCCN, 2022) as well as the Society of Gynecologic Oncologists of the Philippines Treatment Guidelines 2019 (Clinical Practice Guidelines, 2019) recommends neoadjuvant external beam radiation with brachytherapy with or without chemotherapy followed by surgical reassessment. An alternative approach would be the use of neoadjuvant systemic therapy (with a category 2B recommendation) followed by surgical reassessment. (NCCN, 2022).

In terms of surgical management, all patients in this study underwent abdominal extrafascial hysterectomy and bilateral salphingo-oophorectomy as minimally invasive surgery was unavailable. On review of the operative records, 8 patients (57.1%) had pelvic nodal dissection while 5 (35.7%) patients had palpation only during the surgery. Surgical approach was similar with Vargo et al., wherein 33 patients (92%) underwent extrafascial hysterectomy, however, in the study by Iheagwara et al. showed that laparoscopic or robotic-assisted laparoscopic surgery may be a viable option. Minimal surgical morbidities and mortalities were reported in the previous studies.

In terms of systemic therapy, 3 patients (21.4%) in this study received concurrent chemotherapy with radiation followed by adjuvant chemotherapy, while 8 patients (57.4%) received adjuvant chemotherapy only. Two patients did not receive systemic treatment while one received palliative chemotherapy after developing distant metastasis on follow up. Previous studies from Vargo et al., and Iheagwara et al. reported the use of concurrent and concurrent with adjuvant platinum-based chemotherapy in 61 % and 79%, respectively. Chemotherapy was recommended for patients with pretreatment stage III disease or Type II pathology, unless contraindicated. These series justified the use of concurrent chemoradiation in the neoadjuvant setting for endometrial cancer by extrapolating the significant benefits seen in cervical cancer. The role of chemotherapy in the neoadjuvant setting for advanced endometrial cancer has been associated to improve survival when followed by interval debulking surgery. (Khouri et al., 2019 Aug) However, this study by Kouri et al. looked at patients presumed stage III/IV endometrial cancer ineligible for primary surgery. More data is warranted to establish the impact of chemotherapy in the neoadjuvant setting for endometrial cancer patients with cervical and/or parametrial extension. In the adjuvant setting, the PORTEC-3 trial reported an OS and FFS with the addition of chemotherapy which was evident for patients with stage III disease, serous histology and p53 abnormality. (De Boer et al., 2019 Sep) On the other hand, GOG 258 reported that the addition of WPRT with concurrent and adjuvant chemotherapy did not

provide RFS or OS benefit as compared to chemotherapy alone. (Matei et al., 2019 Jun 13) Treatment strategies being explored is a sandwich regimen with radiotherapy "sandwiched" in between chemotherapy cycles. Because of the limited sample size, this study is unable to evaluate the potential significance of chemotherapy on the reported outcomes.

In this study, a total of 14 patients received total neoadjuvant radiotherapy with an external beam radiotherapy (EBRT) dose of 45–50 Gy followed by 4 fractions of 6–7 Gy Point-A based brachytherapy for a median total EQD2 dose of 79.40 Gy (69–81 Gy). This dose is higher compared to the treatment approach reported by Vargo et al., which suggested that an EQD2 of 60–70 Gy may be sufficient for achieving an adequate response before extrafascial hysterectomy. Their findings challenge the previous guidelines that recommend an EQD2 of 75–80 Gy when planning an extrafascial hysterectomy. (Vargo et al., 2014 Nov) Patients then underwent surgical excision wherein 6 (42.9%) out of the 14 patients had pathologic complete response, which is higher as compared to the 15% and 24% from Iheagwara et al and Vargo et al respectively. (Vargo et al., 2014 Nov; Iheagwara et al., 2019 Jul) With a median follow-up of 20 months, only 2 participants (14.3%) had locoregional recurrence, (IQR=18.57 to 22), and 1 (7.1%) had distant recurrence, which is comparable to prior studies which utilized CT based brachytherapy with local control rates ranging from 87.8% in 2 years to 96% in 3 years. (Conway et al., 2019 Oct; Vargo et al., 2014 Nov; Iheagwara et al., 2019 Jul; Gannavarapu et al., 2020 Mar) Same series (Vargo et al., 2014 Nov; Iheagwara et al., 2019 Jul) also showed regional control rates from 81.3 to 89% and distant control rates from 76.3% to 84%. After a median follow-up of 30 months, all participants survived, while 12 (85.7%) had no evidence of any recurrence. On the other hand, reported disease free survival rates range from 52.5% to 73% in three years. Data from modern series also stated overall survival rates of 63.7% to 100% in two to three years(Conway et al., 2019 Oct; Vargo et al., 2014 Nov; Iheagwara et al., 2019 Jul; Gannavarapu et al., 2020 Mar) Our study reported no late grade 3 or higher radiotherapy related complications which is consistent with other series. The toxicities described in other series were mostly late grade 3 radiotherapy-related complications, including bladder complications and bowel obstruction. No grade 4 toxicities were reported in these studies. (Conway et al., 2019 Oct; Vargo et al., 2014 Nov; Iheagwara et al., 2019 Jul).

This study found that patients with grade 1 tumors had significantly increased probability of pathologic complete response ($p = 0.026$). However, there has been no significant association identified between pathologic complete response and age, stage, nodal involvement, initial tumor size (>6cm), histology, EQD2 equivalent dose of > 79.40 Gy and time interval between radiotherapy and surgery of < 45 days. Similarly, in the retrospective series by Vargo et al, pathologic response was not significantly correlated with tumor size (>5cm), histology, EQD2 equivalent dose of > 65 Gy, or concurrent chemotherapy. Further studies with larger sample size investigating factors associated with pathologic response may be warranted.

As of the researchers' knowledge, this is the first study to date that reports on the outcomes of neoadjuvant radiation followed by hysterectomy in locally advanced endometrial cancer in a Filipino cohort. Our findings suggest that results achieved from developed countries can be replicated in low middle income countries using similar protocols.

In addition to the retrospective nature of this study being an inherent limitation, the analysis also included a small sample size and a short median follow-up. The limited sample size could be due to the specific population targeted in the study and impact of the COVID-19 pandemic which has restricted the number of patients receiving surgical management. This study is also unable to report on the complications related to the surgery performed after radiation. Future studies could better assess how upfront radiation followed by extrafascial hysterectomy compares with upfront hysterectomy followed by adjuvant therapy in terms of surgical outcomes and possibly quality of life. The radiation treatment protocols used were also limited by the available technology as the majority were treated with a 2D approach. With the advent of newer techniques, future prospective studies in a similar population with larger sample size may look at improving outcomes with the use of IMRT and image guided brachytherapy, along with longer follow up and surveillance.

5. Conclusion

Our results suggest that neoadjuvant radiation in the form of external beam radiotherapy with HDR brachytherapy followed by hysterectomy with or without chemotherapy is a viable option for endometrial cancer patients with extension to the cervix and parametrium. Upfront radiation may improve resectability resulting in high rates of pathologic complete response and negative resection margins.

6. Disclosures

The project proponent, staff and collaborators of this study have no conflict of interest to disclose.

Credit authorship contribution statement

John Michael P. Tomagan: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Charles Cedy C. Lo:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Alyssa Anne E. Granda:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Mae Mullet Panaligan:** Writing – review & editing, Writing – original draft, Data curation. **Candice Chin-chin C. Yu:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **Veronica T. Vera Cruz:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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