

Survey article

Concurrent chemoradiation versus radiotherapy alone for the treatment of locally advanced cervical cancer in a low-resource setting



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ABSTRACT

Our goal was to determine the clinical treatment response following radiation administered with or without chemotherapy for locally advanced cervical cancers in Honduras. This is a retrospective study of patients treated with either concurrent chemoradiation (CCRT) or external beam radiation therapy (EBRT) alone at a hospital in Tegucigalpa, Honduras. 70 Gy of EBRT to the pelvis was given in all cases. Brachytherapy was not available. Chemotherapy was given when available. Extrafascial hysterectomy was performed 6 weeks after completion of treatment in patients with a complete clinical response (cCR). Records for 165 women with locally advanced cervical cancer were reviewed; 25 (15.2%) stage IB2, 15 (9.1%) stage IIA, 90 (54.5%) stage IIB, and 35 (21.2%) stage IIIB. Ninety (54.5%) patients received EBRT alone; 75 (45.5%) received CCRT. Twenty-three (33.3%) of CCRT patients received weekly cisplatin, the remainder receiving other agents. Seventy (77.8%) of the 90 patients who received EBRT had a cCR; 25 out of 75 (33.3%) patients in the CCRT group achieved a cCR. The CCRT group treated with weekly cisplatin achieved an 80% cCR; while the CCRT group given alternative agents had only a 31% cCR. Patients unable to receive platinum-based CCRT had the worst outcome, and their responses were inferior to patients who received EBRT. The challenges of treating women with locally advanced cervical cancer in a low-resource setting are multifactorial and include treatment delays, the lack of brachytherapy and the unpredictable availability of chemotherapy.

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1. Introduction

Cervical cancer is the fourth most common cancer affecting women worldwide (Ferlay et al., 2010). Globally, there were 527,600 new cases with 265,700 deaths in 2012. Over 85% of cases and 87% of deaths occur in low-resource countries (Siegel et al., 2015). Central and South America are among the regions with the highest incidence (Ferlay et al., 2010), and access to internationally accepted standards of care is often inadequate.

In Honduras, cancer of the uterine cervix is the most commonly diagnosed neoplasm in women. Cervical cancer represents 36.4% of female cancers nationally, and is the principal cause of cancer death in women. In Honduras, cervical cancer most commonly affects women aged 30–69 years and patients are frequently diagnosed with locally advanced disease (Registro hospitalario de cancer 1998–2003, 2004). In

2009, 23% of all cancer cases treated at the Department of Oncology at the Hospital General San Felipe (HGSF) were cervical cancer.

Both surgery and radiotherapy (RT) may be offered as primary treatment in stage I–IIA disease as both treatment options demonstrated similar cure rates in this patient population (Landoni et al., 1997). Standard treatment for patients with more advanced disease is concurrent chemotherapy and external beam RT (EBRT) followed by brachytherapy (Eifel et al., 2004; Morris et al., 1999). Unfortunately this standard treatment is not available in many low-resource settings.

Brachytherapy, a fundamental pillar of treatment for locally advanced cervical cancer, is not available at the National Cancer Center at The Hospital of General San Felipe in Honduras. For this reason, these patients are recommended for EBRT with or without concurrent chemotherapy are utilized. Often, the availability of chemotherapeutic agents is unreliable and EBRT is given alone. Following treatment, those patients with a complete clinical response (cCR) undergo extrafascial hysterectomy in lieu of brachytherapy 4–6 weeks after completion of treatment. Our goal was to evaluate clinical response rates among patients treated in the Department of Oncology at the Hospital

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General San Felipe (HGSE), who received either EBRT alone or concurrent chemoradiation (CCRT) for locally advanced cervical cancer.

2. Materials and methods

After approval from the internal review board, a retrospective chart review was performed for 165 patients who received primary treatment with either EBRT or CCRT for a histologically confirmed diagnosis of cervical cancer at the HGSE from January 2008 to June 2011. Patients older than the age of 20 and younger than the age of 70 were included. Seventy Gray (Gy) of EBRT with or without chemotherapy were given to all the patients. None of the patients received brachytherapy treatment. Patients were deemed to have a clinical complete response (cCR) to RT ± chemotherapy if there was no residual tumor on clinical physical examinations. These patients who had cCR underwent extrafascial hysterectomy 6 weeks after completion of radiation therapy. Data analysis included age, clinical stage, histologic types, size of tumor, date of diagnosis, duration and methods of treatment, and clinical response.

3. Statistical analysis

The primary endpoint of this study was complete clinical response (cCR) upon completion of EBRT and CCRT. Variables with a non-normal distribution were expressed as median and range. For categorical variables, the χ^2 test and the Fisher exact test were used. The *t*-test was used to compare variables that were normally distributed. Comparisons of variables not normally distributed were made by the Mann-Whitney *U* test. *P* values are the result of 2-sided tests and *P* < 0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed with software (SPSS, version 19.0; IBM Corp, Armonk, NY).

4. Results

Patients were collected from January 2008 through June 2011, and 165 women were included in the study. All patients received EBRT or CCRT for stage IB2 through IIIB cervical carcinoma. Ninety patients (54.5%) received EBRT alone and 75 (45.5%) patients received CCRT. The median age, stage, tumor size, and histology were similar in both groups. The treatment duration was significantly longer in the patients who received non-platinum based chemotherapy (Table 1).

Complete clinical response (cCR) rates decreased with advanced stage (Table 2). Stage IIB was the most common stage at diagnosis in both groups with 44/90 (49%) patients in the EBRT group and 38/75 (51%) patients in the CCRT group respectively. The cCR was significantly lower among stage IIB and IIIB patients treated with CCRT when compared with EBRT. Patients with IB2 cervical cancer did equally well and all achieved cCR. Tumor size was >4 cm in 142 (86.1%) of 165

Table 1
Patient characteristics.

	EBRT N = 90 (%)	CCRT N = 75 (%)	<i>P</i> -value
Median age by years (range)	47 (25–64)	44 (27–63)	NS
Stage			0.90
IB2	16 (27)	12 (16)	
IIA	10 (11)	7 (9)	
IIB	44 (49)	38 (51)	
IIIA	0 (0)	0 (0)	
IIIB	20 (22)	18 (24)	
Tumor sizes			0.51
≤4 cm	14 (16)	9 (12)	
>4 cm	76 (84)	66 (88)	
Histology			0.79
Squamous	73 (81)	62 (86)	
Adenocarcinoma	17 (19)	13 (17)	
Treatment duration <60 days	85 (94)	30 (40)	<0.05

(EBRT: external beam radiotherapy; CCRT: concurrent chemoradiation).

Table 2
Complete clinical response rates by stage, tumor size, and histology.

	EBRT (n = 90) number responded (%)	CCRT (n = 75) number responded (%)	<i>P</i> value
FIGO stage			
IB2	13/13 (100)	12/12 (100)	NS
IIA	7/9 (78)	3/6 (50)	NS
IIB	38/49 (78)	9/41 (22)	<0.00001
IIIB	12/19 (63)	1/16 (6)	0.0005
Tumor size			
≤4 cm	14/14 (100)	9/9 (100)	NS
>4 cm	56/76 (74)	16/66 (24)	<0.00001
Histology			
Squamous	56/73 (77)	20/62 (32)	<0.00001
Adenocarcinoma	13/17 (77)	5/13 (39)	NS

FIGO: International Federation of Gynecology and Obstetrics 2009.

patients. All patients with tumors <4 cm experienced cCR, compared to 72 (68.6%) in 142 patients with tumor size >4 cm. Histologic subtype did not appear to be a prognostic indicator: 135 (81.8%) of tumors were squamous cell carcinomas, 30 (18.2%) were adenocarcinomas. Of the 30 cases with adenocarcinoma, 25 (83.3%) underwent treatment with EBRT and 5 (16.7%) received CCRT; of the 135 squamous cell carcinoma (SCC) cases, 73 (54.1%) received EBRT and 62 (45.9%) received CCRT. Overall 76/135 patients with SCC demonstrated 56.3% cCR rate, which was comparable to the cCR of 18/30 (60%) among adenocarcinoma cases. The cCR of 33.3% were significantly lower in both SCC and adenocarcinoma patients who received CCRT comparing to the cCR of 76.7% for those who received EBRT (Table 2).

Overall, cCR was seen in 95 patients (57.6%) in both groups combined. Of the patients who were treated with CCRT, 23 patients (33.3%) were treated with cisplatin (40 mg/m² weekly for 5 cycles) chemotherapy and the remaining 52 patients (66.7%) received 5-fluorouracil (700 mg/m² day 1–4 every 3 weeks), capecitabine (1000 mg/m² twice daily on days 1 to 14, every 3 weeks for 2 cycles) or gemcitabine (1000 mg/m² on days 1 and 8, every 3 weeks for 2 cycles). Of the 90 patients who received EBRT alone, 70 patients had a cCR of 77.8% and underwent adjuvant hysterectomy. In the CCRT group, 25 patients (33%) had a cCR (Fig. 1A). The 25 patients that received cisplatin based therapy demonstrated an 80% cCR rate (Fig. 1B). Residual tumors were found in 50% of the patients who underwent hysterectomy in both groups.

One hundred and fifteen (69.5%) of patients completed their treatments within 60 days. The cCR was 65.2% in this group of patients. The treatment duration was significantly longer in the patients who received non-platinum based chemotherapy (Table 1). Of the 23 patients who received CCRT with cisplatin, only 5 patients had their treatments extended beyond 60 days. The majority of the CCRT patients that had treatment longer than 60 days received other agents (5-fluorouracil, capecitabine and gemcitabine). These patients had a poor cCR of 31% (Fig. 1B). There were no differences between the two groups in the incidence of grade 3 and 4 toxicities: 13% in the EBRT group and 19% in the CCRT groups (NS).

5. Discussion

The burden of cervical cancer continues to fall most heavily on low- and middle-income countries largely due to lack of screening and treatment modalities. In a high-resource setting, the standard of care for locally advanced cervical cancer is CCRT with cisplatin based chemotherapy followed by brachytherapy (Eifel et al., 2004; Morris et al., 1999; Souhami et al., 1991; Tattersall et al., 1995; Rose et al., 1999). Although it has previously been demonstrated that non-platinum based chemotherapy regimens are less effective (Eifel et al., 2004; Morris et al., 1999; Tattersall et al., 1995; Rose et al., 1999; Whitney et al., 1999), platinum-based chemotherapy may not be readily available in

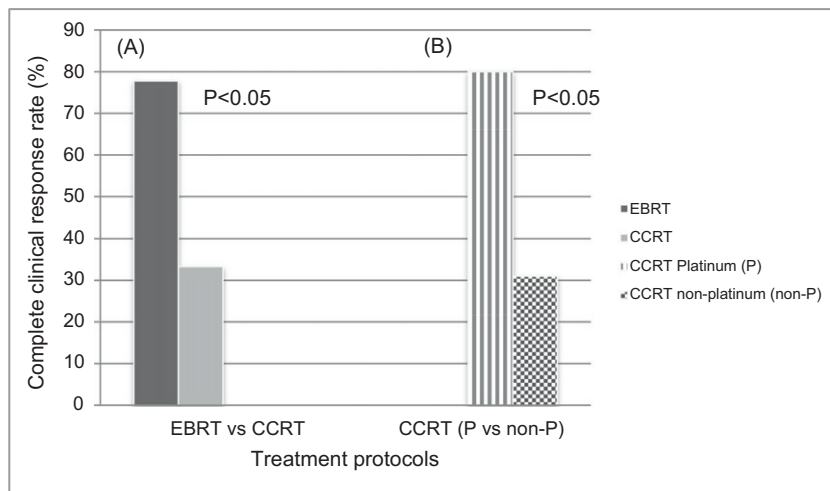


Fig. 1. Clinical response rates by treatment protocols.

low-resource settings. This was the case in the patient population at HGSF in Honduras, and as would be expected, patients who received non-platinum based therapy had lower response rates. Approximately two-thirds of the patients in this cohort received non-platinum based CCRT with only a 31% response rate. Among the patients in this study who received platinum based therapy, the response rates were comparable to those cited in the literature. This emphasizes the importance of platinum based regimens in the treatment of locally advanced cervical cancer.

Brachytherapy following concurrent chemotherapy and EBRT is considered standard of care, but brachytherapy is not available at the HGSF and we therefore substituted adjuvant extrafascial hysterectomy for this modality. The role of adjuvant extrafascial hysterectomy has been explored by the Gynecologic Oncology Group (GOG) in patients with bulky FIGO stage IB invasive carcinoma of the cervix. They reported on a cohort of patients with tumors measuring >4 cm who were randomized to extrafascial hysterectomy or observation following EBRT and brachytherapy (chemotherapy was not administered in either arm). In this cohort there was a lower rate of local relapse (14% vs. 27% at 5 years) in the hysterectomy group. However, overall survival outcomes were not statistically different between the two groups (Keys et al., 2003). Although our patients did not have brachytherapy available to them, we felt that this GOG data supports the use of adjuvant extrafascial hysterectomy in these patients. Our study was not designed to assess survival, but this will be the subject of future analysis.

Factors associated with treatment failure in patients with cervical cancer include large volume of disease and treatment prolongation. The best response was seen among smaller tumors at less advanced stages in our patient population. All patients with tumors measuring 4 cm or less had a favorable response. In comparison, only 50.7% of patients with tumors measuring >4 cm had a clinical complete response. With regards to treatment time, it has been shown that a protracted treatment course can be deleterious to overall outcomes (Fyles et al., 1992; Petereit et al., 1995; Perez et al., 1995). One group demonstrated that survival and pelvic control at 5 years decreased 0.6% and 0.7%, respectively, for each additional day of treatment beyond 55 days (Petereit et al., 1995). In our patients treatment can be delayed for reasons including lack of financial resources, difficulty with transportation and various socioeconomic stressors. These treatment delays likely contribute to a reduction in the cCR and once radiotherapy is initiated every effort should be made not to delay treatment.

Cervical cancer is the most commonly diagnosed cancer among women in Honduras. To this end, these women deserve the opportunity

to receive a therapy with the goal of achieving cure. Efforts should be made to treat women with locally advanced cervical cancer with cisplatin-based CCRT. Treatment should not be delayed once it has been initiated and if cisplatin is not available, radiotherapy should be offered rather than delay treatment while awaiting availability of chemotherapy agents.

Disclosure

None of the authors have any potential conflicting interests to declare.

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