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Cervical cancer treatment in Haiti: A vertically-integrated model for low-resource settings

Vincent DeGennaro
Herbert Wertheim College of Medicine, Florida International University; Innovating Healthy International, vdegenna@fiu.edu

Madelyn Shafer
George Washington University

Meagan Kelly
University of Florida

Jean Ronald Cornely
Ministry of Public Health, Port-au-Prince, Haiti

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Review article

Cervical cancer treatment in Haiti: A vertically-integrated model for low-resource settings

Vincent DeGennaro Jr[a,b,*], Madelyn Shafer[c], Meagan Kelly[d], Jean Ronald Cornely[e], Joseph Bernard Jr[a]

[a] Innovating Health International, Port-au-Prince, Haiti
[b] Department of Medicine, Florida International University College of Medicine, Miami, FL, United States of America
[c] Milken Institute School of Public Health, George Washington University, WA, United States of America
[d] University of Florida College of Medicine, Gainesville, FL, United States of America
[e] Oncology Division, Ministry of Public Health, Port-au-Prince, Haiti

1. Introduction

Cancer is a leading cause of death worldwide. In 2012, the incidence of cancer was estimated to be 14 million cases with 8 million cancer-related deaths (Stewart et al., 2015). 1.7 of the 14 million cases of cancer in 2012 were cervical cancer with over 500,000 deaths (Torre et al., 2016). In 2016 approximately 90% of all deaths from cervical cancer happened in low-income and middle-income countries (Knaul et al., 2019). The high mortality rate of cervical cancer in low-income countries is often attributed to lack of access to screening and prevention efforts, not to an inability to provide treatment (Gyawali and Iddawela, 2016). A large proportion of cervical cancer patients in low-income countries present at an advanced stage (Sankaranarayanan et al., 2010) and our cancer treatment program in Haiti, operated by the non-profit Innovating Health International (IHI), is representative of this phenomenon. With limited resources, IHI manages a vertically-integrated approach towards cervical cancer treatment combining a widespread screening campaign, awareness programs, chemotherapy and surgery.

Screening is an integral component of reducing the risk of cervical cancer for women. Low-cost, evidence-based, alternative screening methods are often applied to limited resource settings. This includes the single visit approach referred to as the “screen and treat” method, with uses VIA combined with cryotherapy or thermocoagulation (Ardahan and Temel, 2011). Of many studies conducted, VIA consistently has a higher rate of sensitivity when contrasted with Pap smear (Ardahan and Temel, 2011; Saleh, 2014). Because vaginal HPV swabs are preserved indefinitely at room temperature and may be shipped from anywhere in the country to a laboratory there is great potential for this screening method in low resource settings.

Radiotherapy has been found to benefit at least 50% of all cancer patients (Atun et al., 2015; International Atomic Energy Agency, 2014) but little international funding is committed to increasing access in low-income countries. Limited resources prohibit these countries from implementing radiation due to lack of infrastructure, lack of reliable electricity, variable security, and geopolitical instability (Barton et al., 2014). There is a world-wide shortage of radiotherapy with up to 90% of low-income populations lacking access to these resources (Gajjar et al., 2018a). Without radiotherapy in Haiti (Gajjar et al., 2018a), IHI has begun to implement neoadjuvant chemotherapy to expand the potential for treatment for cervical cancer patients. Chemotherapy is considered safe in the treatment of cervical cancer and is less expensive than radiotherapy (Smith and Rutledge, 1975). As of April 2018, the Dominican Republic retired its last cobalt machine, the use of which cost $2000 per treatment, per patient. Of note, linear accelerator treatment costs over $10,000 per patient, far outside the reach of NGOs and most Haitians.

Studies of neoadjuvant chemotherapy (NACT) have shown success in implementing cisplatin and paclitaxel as a first line treatment for advanced stages of cervical cancer (Moore et al., 2004; *Electronic Medicines Compendium: Doxorubicin 2 mg/ml Concentrate for Solution for Infusion: Summary of Product Characteristics*, 2014). NACT with cisplatin and paclitaxel has the ability to eliminate or shrink the primary tumor and allow procession to radical hysterectomy (Kim et al., 1989). Many studies have found NACT to have a response rate of higher than 80% (Yamaguchi et al., 2012). In one study of 54 patients that received chemotherapy followed by radical hysterectomy, 81% of patients had a histological response to treatment and 94% of patients were tumor free at two years (Kim et al., 1989). One recent meta-analysis consisting of 872 patients showed a 35% mortality risk reduction with the use of NACT followed by surgical intervention compared to radiation therapy alone (Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration, 2003). This study displayed a 14% improvement in 5 year survival with a survival rate of 64% for patients with advanced stages of cervical cancer (Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration,

* Corresponding author at: 1120 SW 8th Street, AHC2, Miami, FL 33199, United States of America.
E-mail address: innovatinghealthinternational@gmail.com (V. DeGennaro).

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2003). Based on these studies, new resource-stratified guidelines from the American Society of Clinical Oncology recommend NACT followed by hysterectomy for cervical cancer stages II-IV for women in countries that do not have access to radiotherapy (Chuang et al., 2016a).

There is a great need for further investigation into alternative cervical cancer screening and treatment methods in low resource countries. The disparity in cervical cancer deaths between low income countries such as Haiti and the rest of the developed world is alarming. This report reviews screening and treatment methods at IHI's programs in Haiti and navigates the components of our vertically-integrated cervical cancer screening and treatment program. We will describe the results of three separate components of the program: screening, chemotherapy, and surgery.

2. Methods

2.1. Screening

IHI and the Haitian Ministry of Health have initiated the "screen and treat" method at 10 public hospitals throughout Haiti. Additionally, IHI has implemented an employment-based program using vaginal self-swabs for high-risk HPV followed by thermocoagulation for those who test positive (DeGennaro Jr et al., 2015a). This initiative takes place in factories where women work six days a week across the country. In this way, screening is brought into the community for women who would not otherwise have access to care. In both projects, IHI utilizes Haitian community health workers (CHWs), nurses, and community leaders to provide health education to these women. Increasing evidence has shown that education provided by native CHWs is more effective, fosters community engagement and improves health outcomes in rural areas that lack typical screening and treatment facilities (Glanz et al., 2008).

For the hospital VIA program, patients completed a basic medical history form before each exam. The results of exams and follow up visits were recorded on paper as well. Patient data was collected from each of the clinics and entered into a secure computer database. Nurses took photos of the data sheets to ensure proper data entry back at our main office in Port au Prince. Original paper forms were left at the partner hospitals.

2.2. Chemotherapy

Since 2013, IHI has trained 32 Haitian physicians and 50 Haitian nurses in general cancer care from diagnosis to treatment, including the mixing and administration of chemotherapy. Training includes intensive classroom education on cervical cancer pathophysiology, presentation, diagnosis, and treatment using chemotherapy treatment algorithms (Santamaria et al., 2016) and training in performing core needle biopsies. Core biopsies were performed instead of punch biopsies because supplies for the latter are not as readily available. We believe that this substitution does not significantly or negatively impact patient care. In collaboration with the Ministry of Health, we have administered chemotherapy at five different hospitals across the country, although we principally treat at an outpatient cancer center in Port-au-Prince.

A chart review of our patients with a pathological diagnosis of cervical cancer from June 1st, 2016 to May 31st, 2018 was performed and the following key variables were extracted: age, FIGO classification, histological type, grading, obstetrical history, contraception use, tobacco use, HIV status and clinical outcome. These variables were then evaluated to determine their association with mortality. Tissue was reviewed in a pathology lab in Port au Prince or Cap Haitien.

Once the diagnosis of cervical cancer was established via biopsy and local interpretation patients met with Haitian physicians on site for treatment. Treatment plans were developed depending on cancer stage and grade. Typically patients received 75 mg/m^2 cisplatin with or without 175 mg/m^2 paclitaxel every three weeks for a total of one to six cycles depending on FIGO stage and clinical response. Patients were monitored with CBC and creatinine every three weeks. Patient information was recorded upon consultation and throughout treatment. After completion of treatment, patient information was entered into a computerized file system.

2.3. Radiation therapy

Occasionally, NGOs such as IHI, are able to assist a small number of patients to receive radiotherapy in the Dominican Republic (Santamaria et al., 2016). Out of the152 patients seen the past two years at IHI for cervical cancer, only three were able to receive radiation therapy. Unfortunately, not all were able to complete treatment due to cost and logistics.

2.4. Surgery

IHI has successfully organized five surgical trips during which foreign gynecologic oncologists traveled to Haiti to train and operate with Haitian OB GYNs. Ideal patient criteria to be eligible for surgery included having stage IB2, II or III cervical cancer, having completed at least three cycles of NACT and having a hemoglobin $>$ 9 g/dL at the time of operation. Ideally all patients with stage 2 or 3 cancer would have gotten at least 3 cycles of NACT before surgery. There were 3 exceptions in which patients received only 1–2 cycles of NACT, usually due to timing of when surgical teams would be in country. If deemed resectable at that time, they proceeded to surgery. Others with IB2 didn't warrant chemotherapy according to our protocol, but received it as a means of temporizing the cancer while we waited up to three months for a surgical team to come. After careful review of each patient's case and the risks/benefits the decision was made to proceed with surgery in the interest of the patient. Patients were monitored in the postoperative period by our IHI OB GYNs, both immediately and for follow up. They communicated by telephone or text with the visiting surgeon as needed. Two Haitian OB GYNs consistently operated with the visiting surgeons, with the goal of training them to perform radical hysterectomies independently. The project is ongoing. There are very few Haitian OB GYNs who are trained to perform radical hysterectomies, especially when the indication is for malignancy. The intention of this program was to provide this training while treating patients. The Haitian OB GYNs chosen to be involved in this program have finished residency, studied oncology with IHI, and have been administering chemotherapy for 3 years as part of IHI's cancer treatment program. They are the OB GYNs with the most oncology training in the country who expressed an interest in advancing their surgical skills. Providing them with an opportunity to learn radical hysterectomy has the potential to substantially impact patient care. The goal is to have each surgeon perform at least 25 operations before working independently.

3. Results

3.1. Screening program

A retrospective review of data from IHI and its partner facilities indicates that 4556 patients have undergone the VIA "screen and treat" method over a 2-year period ending in June 2018. Of those, 840 women (18.4%) were positive and treated with cryotherapy or thermocoagulation. This percentage is similar to other studies in low income settings. One such study in India found a VIA positivity rate of 10.75% (Poli et al., 2015). The average age of patients seen in clinic for the "see and treat" method was 38.9 years old. Through this program, 59 Haitian nurses/midwives and 10 Haitian physicians have been trained in the "see and treat" method with cryotherapy or thermocoagulation. Patients with lesions covering $<$ 75% of the cervix and without

Table 1
Baselines characteristics of the study population.

Variables	Frequency (n)	Proportion (%)	95% Confidence Interval
Age at Presentation (N = 152)			
30–39	17	11.2%	6.7%–17.3%
40–49	45	29.6%	22.5%–37.5%
50–59	44	28.9%	21.9%–36.9%
60–69	28	18.4%	12.6%–25.5%
70–79	13	8.6%	4.6%–14.2%
≥80	5	3.3%	1.1%–7.5%
Stage at Presentation (N = 126)			
0 (In situ carcinoma)	8	6.3%	2.8%–12.1%
IA	1	0.8%	0.02%–4.3%
IA1	1	0.8%	0.02%–4.3%
IB1	4	3.2%	0.9%–7.9%
IB2	5	4.0%	1.3%–9.0%
IIA	6	4.8%	1.8%–10.1%
IIB	20	15.9%	10.0%–23.4%
IIIA	29	23.0%	16.0%–31.4%
IIIB	15	11.9%	6.8%–18.9%
IVA	29	23.0%	16.0%–31.4%
IVB	8	6.3%	2.8%–12.1%
Risk Factors			
Tobacco use (N = 143)	15	10.5%	6.0%–16.7%
History of abortion (N = 145)	55	37.9%	30.0%–46.4%
Teenage pregnancy (N = 78)	39	50.0%	38.5%–61.5%
Children with > 1 man (N = 84)	57	67.9%	56.8%–77.6%
Family history of cancer (N = 97)	18	18.6%	11.4%–27.7%
Baseline ECOG (N = 113)			
0	92	81.4%	73.0%–88.1%
1	14	12.4%	6.9%–19.9%
2	4	3.5%	0.97%–8.8%
3	1	0.9%	0.02%–4.8%
4	2	1.8%	0.2%–6.2%
HIV status (N = 152)			
HIV-positive	12	7.9%	4.1%–13.4%
HIV-negative	66	43.4%	35.4%–51.7%
Unknown	74	48.7%	40.5%–56.9%
Recurrent case (N = 152)			
Yes	10	6.6%	3.2%–11.8%
No	142	93.4%	88.2%–96.8%
Histologic subtype (N = 126)			
Squamous cell carcinoma	105	83.3%	75.7%–89.4%
Adenocarcinoma	12	9.5%	5.0%–16.1%
In situ carcinoma	8	6.3%	2.8%–12.1%
Adenosquamous carcinoma	1	0.8%	0.02%–4.3%
Histologic grading (N = 90)			
Grade 1	21	23.3%	15.1%–33.4%
Grade 2	53	58.9%	48.0%–69.2%
Grade 3	16	17.8%	10.5%–27.3%
Outcome (N = 152)			
Alive/in treatment	98	64.5%	56.3%–72.1%
Deceased	38	25.0%	18.3%–32.7%
Lost to follow-up	16	10.5%	6.1%–16.5%

endocervical involvement were eligible for thermocoagulation. Thermocoagulation was typically performed by our trained IHI nurses. If the patient had a lesion > 75% of the cervix or there was extension into endocervix, they were referred to an IHI OB GYN for performance of a LEEP.

As part of our awareness program, 33,258 people were educated on cervical cancer through in-person outreach events. This included lectures given by CHWs and cancer survivors at churches and schools and volunteers going door to door in their neighborhoods. There is no way to quantify the number of people reached through television and radio interviews as well as social media outreach, but it likely doubles that which we were able to reach in person.

3.2. Chemotherapy program

A total of 152 cases of cervical cancer were managed during the study period. 6.6% of them were recurrent malignancies. The median age of the study population was 52.5 years old with a range of 30–90 years old (Table 1). 10.5% (n = 143) of the patients admitted to tobacco use. 62.8% of the women (n = 145) were post-menopausal and 37.9% (n = 145) had a history of abortion. Of those with known HIV status (n = 78), 15.4% were seropositive. Of those patients with FIGO classification recorded (n = 126), 80.1% were Stage IIB or higher, and 29.3% were Stage IV. Tissue pathology varied with 83.3% invasive squamous cell carcinoma, 9.5% adenocarcinoma, 6.3% in situ squamous carcinoma and 0.8% adenosquamous carcinoma. The overall mortality rate was 25.7% over 24 months, and 10.5% of the patients were lost to follow-up. Much like in our breast cancer program, we have not had any serious complications related to giving chemotherapy, including those who are HIV program (DeGennaro Jr et al., 2015b).

Of the advanced cases of cervical cancer, 17 patients received neoadjuvant chemotherapy with cisplatin and paclitaxel before a planned radical hysterectomy, 2 received chemoradiation therapy outside of Haiti, 31 received palliative chemotherapy with cisplatin only and 46 received palliative care only (Fig. 1).

3.3. Surgery program

A total of 16 patients were identified as eligible for surgery and brought to the operating room. Of them, 7 had a radical hysterectomy, 6 had simple hysterectomies, and 3 were open and close procedures due to obvious metastatic disease (Table 2). All those who underwent hysterectomy were thought to have clinically negative margins. Simple hysterectomy is considered the standard of care for stage IB2 patients in low income countries per ASCO guidelines (Wu et al., 2017; Chuang et al., 2016b). We had 2 patients with cancer beyond IB2 who had simple hysterectomies (IIA and IIB). The decision of simple versus radical hysterectomy was ultimately made by the surgeon based on preference and patient safety. 25 of our patients had stage IIA or less. These patients were referred out to other community OB GYNs who are capable of doing simple hysterectomies. We did not continue to follow them clinically.

The most recent two surgical trips comprised 11 of the 16 total procedures, indicating that the program is growing in efficiency and that the need for radical hysterectomies post-NACT is apparent in this community. One intraoperative complication, damage to the inferior vena cava and left common iliac vein, occurred. All patients were alive at least 12 months from the date of their operation with no post-operative complications, and we will continue to follow them. Evidence of disease is determined clinically since routine CT scans are too expensive for the program's resources. One patient who had obvious metastases noted in surgery was still living 12 months later without other interventions. Deciding whether there is evidence of disease after treatment is determined clinically in follow up.

4. Discussion

In low-resource settings, providers are challenged to adapt cost-effective and culturally competent methods of delivering healthcare. We have presented a vertically-integrated model for cervical cancer prevention, screening and treatment in Haiti. At each phase of our program, we have made adaptations from the typical methods available in high and middle-income countries. We have encountered countless barriers, chief among them being cost. IHI never refuses to care for a patient due to lack of finances. Because improving access to quality care

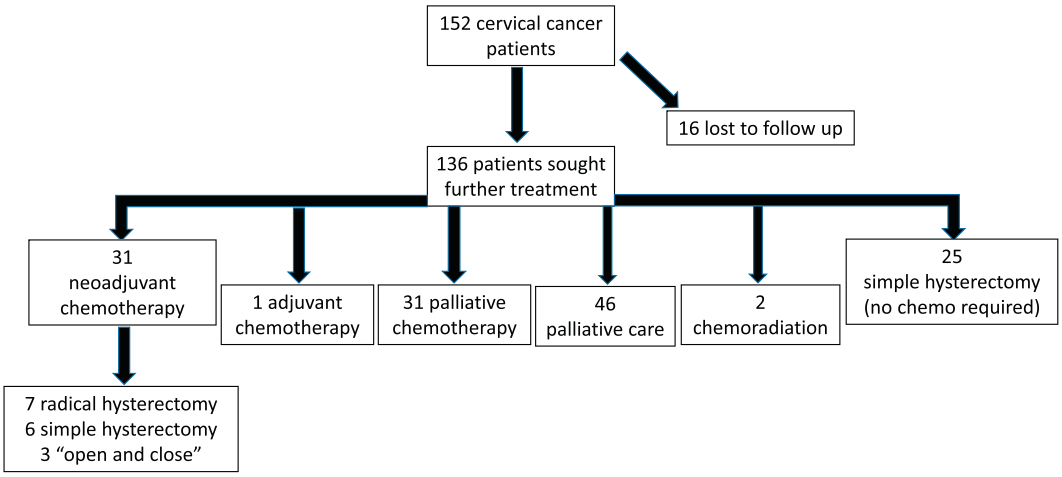

Fig. 1. Patient flow chart.

is our ultimate goal, we individualize services based on the patient situation, which may include coverage for things such as transportation to the clinic, nutrition and clothing. Only approximately 25% of our treatment costs come from patient payments.

Our cohort of women with cervical cancer undergoing chemotherapy was relatively young, with 40.8% < 50 years of age. The prevalence of tobacco use (10.5%) in this population was more than twice that of Haitian women in general and nearly twice that of tobacco use in Haitian women with breast cancer (DeGennaro Jr et al., 2018a; DeGennaro Jr et al., 2018b). The prevalence of HIV in this population was 15.4%, much higher than the overall HIV prevalence in Haiti of 2.1% (Unicef, 2013). While most women had Stage III or IV cancer (64.2%), 93.8% were highly functional with an ECOG of 0 or 1.

Training Haitian staff continues to be the highest priority in all of our programs. At this point, only the surgical program requires outside specialists. The majority of people involved in our program live in Haiti and are fluent in Creole. We are an intimate part of the community and culture. For our incoming surgeons, we have translators available for the operating room as needed and the OB GYNs speak English. The head nurse of our screening program travels to the all of the sites to ensure the quality of VIA and thermocoagulation/cryotherapy treatments. This portion of the program has been nurse-led for 3 years, they are well trained, and task shifting is quite common and indeed necessary in low-income settings. The head nurse helps with raising local awareness of the program and works in the community with the ultimate goal being independent support of the program. There is high turnover of nursing staff at Haitian hospitals, which has been a challenge. We have had to train new staff members in VIA with cryotherapy or thermocoagulation at two of the partner hospitals. We are also currently training another Haitian internist in oncology. Her education involves a mix of didactics, supervised patient encounters, and telemedicine.

Data collection, entry and management has been a challenge for our screening program. Because each site is a public hospital, we have tried not to implement onerous, new documentation requirements. In the future, we hope to use optical character recognition (OCR) capture software to speed data entry, improve data fidelity, and lower nursing travel costs. Our onsite nurses typically have smartphones and could potentially upload images of clinical patient forms using OCR technology. This would both lower costs associated with nurse visits to sites simply to collect data and increase data accuracy.

Supply chain management is another constant challenge in this program. Nurses at many of our sites do not have access to computers and must rely on non-electronic forms of inventory control. OCR forms for inventory would allow them to use pencil and paper and then capture and send the image to the coordinating team in Port au Prince without the need for a computer. In addition, we have started to procure all supplies in large volumes for six-month blocks to decrease cost, reduce manpower for procurement, and ensure adequate stock.

Table 2
Characteristics of surgical cases.

Patient	Age	Histology	Pre-op stage	Cycles of NACT	Procedure performed
1	47	SCC cervix	IIB	2	Type III radical hysterectomy, BSO, LND
2	56	SCC cervix	IIIA	3	Open and close, metastasis in omentum and right pelvis
3	56	SCC cervix	IIB	2	Simple hysterectomy with small upper vaginal margin, BSO, LOA
4	62	Adenocarcinoma cervix	IIB	6	Metastasis noted, R salpingo-oophorectomy for pathology
5	68	SCC cervix	IIB	5	Type II modified radical hysterectomy, BSO, LOA
6	63	SCC cervix	II	3	Open and close due to metastasis
7	54	SCC cervix	IIIA	3	Wetheim-Meigs operation (Querleu C), bilateral pelvic and retroperitoneal lymphadenectomy, IVC injury, Left Common Iliac Vein Injury
8	49	SCC	IIIA	4	Wetheim-Meigs operation (Querleu B2), bilateral pelvic and retroperitoneal lymphadenectomy
9	31	SCC	IIIA	3	Wetheim-Meigs operation, bilateral pelvic and retroperitoneal lymphadenectomy, mass in left iliac vessels, lymph nodes in retroperitoneum
10	74	SCC	IIIA	6	Wetheim-Meigs operation (Querleu C) and bilateral pelvic lymphadenectomy
11	62	SCC	IIA	3	Simple hysterectomy
12	61	SCC	IIIA	1	Wetheim-Meigs operation (Querleu C) and bilateral pelvic and retroperitoneal lymphadenectomy
13	53	SSC	IB2	3	Simple hysterectomy, LND
14	46	Papillary adenocarcinoma	IB2	3	Simple Hysterectomy, LND
15	45	SCC	IB2	3	Simple Hysterectomy, LND
16	55	SCC	IIB	3	Simple Hysterectomy, LND

As is the case with much of global health, our chemotherapy protocols were partly determined based on availability of resources. For example, carboplatin is significantly more expensive than cisplatin and has largely been substituted. In patients who were staged clinically before and after chemotherapy, there was an overall decrease in their stage. Unfortunately, our sample size is too small to determine statistical significance in improvement of tumor burden or operability after chemotherapy.

The American surgeons who have participated in our program have come from both private and academic settings, allowing for a diversity of training in operative approaches for our Haitian OB/GYNs. We are currently testing adoption of standard US operating room practices such as pre-operative check lists, standard operating procedures, case logs, and other items to ensure quality surgical and anesthesia care.

Perhaps the most important aspect of our program is the vertical integration of screening, chemotherapy and surgery. Haiti has a fragmented healthcare system that is difficult to navigate for those with an education and means but can be literally impossible for those who are uneducated and poor. By referring patients directly from IHI-partnered screening sites to the IHI Women's Cancer Center, we decrease loss to follow up and can offer care to those who cannot afford it.

5. Conclusion

Awareness campaigns, “see and treat” screening methods, and collaborations with public institutions have all helped IHI develop a vertically-integrated cervical cancer program. Due to these efforts there has been a significant increase in patients seeking screening and treatment. As screening and treatment for cervical cancer increases, the hope is to make more treatment methods available in the future. Of note, we have an analogous initiative for breast cancer, which has had great success (DeGennaro Jr et al., 2018a; Gajjar et al., 2018b; DeGennaro Jr et al., 2015b). IHI is hopeful that likewise this developing program will bring new opportunities for cancer care in low-income countries.

Conflict of interest statement

We have no conflicts of interest. Work Supported by Gloria Gifford Scully Memorial Fund and Innovating Health International.

Author contributions

Meagan Kelly – Ran surgical trip, manuscript writing.

Jean Ronald Cornely – manuscript editing.

Madelyn Shaefer – manuscript writing, data collection, data analysis.

Joseph Bernard - study design, data collection, data analysis.

Vincent DeGennaro - study design, data collection, data analysis, manuscript editing.

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