Neoadjuvant chemotherapy in pregnant patients with cervical cancer: a Latin-American multicenter study

Aldo Lopez,[1] Juliana Rodriguez ,[2,3] Erick Estrada,[4] Alejandro Aragona,[5] Carlos Chavez,[6] Karina Amaro,[7] Cristiano De Padua,[8] Alfredo Borges Garnica,[9] Gabriel Rendón ,[10] Adriana Alméciga ,[2] Oscar Serrano,[11] Santiago Scasso,[12] Joel Laufer,[12] Diego Greif,[13] Fernando Taranto,[13] Jorge Hoegl,[14] Franco Calderaro di Ruggiero,[14] René Pareja [2,15]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2020-001764).

For numbered affiliations see end of article.

Correspondence to
Dr René Pareja, Gynecology and Gynecologic Oncology, Clinica ASTORGA, Medellin, and Instituto Nacional de Cancerología, Medellin 1234, Colombia; ajerapener@gmail.com

Received 15 September 2020
Revised 10 December 2020
Accepted 11 December 2020

To cite: Lopez A, Rodriguez J, Estrada E, *et al. Int J Gynecol Cancer* 2021;**31**:468–474.

HIGHLIGHTS

- Cervical cancer during pregnancy was primarily diagnosed at early stage (60.6%).
- The use of neoadjuvant chemotherapy during pregnancy can be considered an alternative in order to achieve fetal lung maturity.
- Recurrence rate was 26.7% in patients undergoing neoadjuvant chemotherapy during pregnancy.

ABSTRACT

Objective To describe oncologic and obstetric outcomes in patients diagnosed with cervical cancer during pregnancy who had a successful delivery after neoadjuvant chemotherapy.

Methods A multicenter retrospective review was conducted in 12 institutions from six Latin American countries, between January 2007 and December 2018. Data collected included clinical characteristics, neoadjuvant chemotherapy agents, treatment, obstetric and oncologic outcomes.

Results Thirty-three patients were included. Median age was 34 years (range 31–36). Twenty (60.6%) women were diagnosed at early stage (IB), and 13 (39.4%) with locally advanced stage (IIA–IIIB) according to FIGO 2009 classification. Carboplatin and paclitaxel was the most frequent combination used (60.6%). Partial and complete response rates were 27.3% and 9.1%, respectively. Median gestational age at delivery was 35 weeks (range 34–36). All patients had live births delivered by cesarean section. Obstetric pathology: pre-term labor, placenta percreta or intrauterine growth restriction, was documented in seven patients (21.2%). Two (6.1%) neonates had low birth weight. Definitive treatment was primary chemo-radiation in 19 (57.6%) patients, radical hysterectomy in 11 (33.3%), abandoned radical hysterectomy with para-aortic lymphadenectomy and ovarian transposition in 1 patient (3.0%), and no further treatment in 2 (6.1%) patients. After a median follow-up of 16.3 months (range 2.0–36.9), 8 (26.7%) patients had recurrent disease. Of these, four (13.3%) died due to disease.

Conclusion Neoadjuvant chemotherapy may be offered to patients wishing to preserve an ongoing pregnancy in order to achieve fetal maturity. Long-term consequences of chemotherapy in the child are yet to be determined.

INTRODUCTION

Cervical cancer ranks third in incidence and mortality among women worldwide, with 569 847 new cases and 311 365 deaths per year. In South America and the Caribbean, cervical cancer ranks second and third in incidence and mortality respectively, with 56 187 new cases and 28 318 deaths.[1] A diagnosis of cervical cancer, can lead to complications in approximately 0.05–0.1% of all pregnancies.[2] The most frequent malignancy diagnosed during pregnancy is breast cancer, followed by cervical cancer, hematological malignancies, and melanoma, accounting altogether for 70% of cancers during pregnancy.[3] Cervical cancer is the most common gynecologic malignancy diagnosed during pregnancy, with an incidence of 1.4 to 4.6 per 100 000 pregnancies; overall 3% of all cervical cancer cases are diagnosed during pregnancy.[4] Chemotherapy has been traditionally associated with potential teratogenic risk on early pregnancy and intrauterine growth restriction in second and third trimesters.

The final decision about the treatment of cervical cancer during pregnancy must be based on lymph node involvement, tumor size, histological subtype. Among the therapeutic options are delaying definitive treatment until delivery, immediate termination of pregnancy, intentional pre-term delivery to start primary management, and others such as surgical treatment (conization or simple/radical trachelectomy, with/without lymphadenectomy), and neoadjuvant chemotherapy while gestation is preserved.[5]

Literature on neoadjuvant chemotherapy during pregnancy is limited, as shown by the fact that a recently published meta-analysis included only 88 patients.[6] In their conclusion, the authors stated that neoadjuvant platinum-based chemotherapy could be a favorable option during second and third trimesters in patients with cervical cancer without any apparent associated morbidity to newborns.

Our aim was to report the oncologic and obstetric outcome of patients diagnosed with cervical cancer during pregnancy who achieved a successful delivery after receiving neoadjuvant chemotherapy.

METHODS

A multicenter retrospective review was conducted including all patients with confirmed histopathological diagnosis of FIGO 2009 stage IB1–IVA cervical cancer during pregnancy, who received neoadjuvant chemotherapy prior to definitive cancer treatment and had a successful delivery between January 2007 and December 2018. Patients were included at 12 institutions from six Latin American countries: Instituto Nacional de Enfermedades Neoplásicas, Perú; Instituto Regional de Enfermedades Neoplásicas – Arequipa – IREN SUR, Perú; Hospital Cayetano Heredia, Perú; Instituto Nacional de Cancerología, Colombia; Hospital Militar Central Colombia; Instituto de Cancerología- Las Américas-AUNA, Colombia; Unidad de Terapia Antineoplásica (UTAN,Centro Médico Guerra Méndez Valencia, Venezuela; Hospital Oncológico de Buenos Aires Marie Curie, Argentina; Hospital de Cáncer de Barretos, Brazil; Hospital Pereira Rossell, Uruguay; Clínica Médica Uruguaya Uruguay; Servicio Oncológico Hospitalario de Caracas, Venezuela. Patients with up-front surgery, treatment delayed until delivery, induction of labor and subsequent treatment were excluded. We also excluded patients with spontaneous termination or stillbirth associated with neoadjuvant chemotherapy.

All patient information was collected, ensuring confidentiality, by the principal investigator in each of the centers. These data were obtained from the maternal and neonatal medical history. Clinical characteristics (age, histology, tumor size, gestational weeks at diagnosis), type of images obtained during neoadjuvant chemotherapy (MRI, abdominal ultrasound), neoadjuvant chemotherapy (agents, number of cycles, gestational age to treatment, toxicity, imaging response), obstetric, perinatal and neonatal outcomes, definitive treatment modalities, and oncological outcomes were recorded. Follow-up during neoadjuvant chemotherapy was by physical examination and imaging at discretion of the treating physician. A maternal–fetal medicine specialist monitored patients in all countries.

The pregnancy trimesters were defined as first trimester (0–14 weeks), second trimester (15–28 weeks), third trimester (29–42 weeks). The tumor size was defined on clinical examination. The tumor size response was based on the RECIST 1.1 response criteria.[7] For obstetric outcomes, intrauterine growth restriction was defined according to the American College of Obstetricians and Gynecologists[8] and the Royal College of Obstetricians and Gynecologists,[9] as estimated fetal weight in the 10th centile or less. Low birth weight was defined according to the World Health Organization[10] as weight at birth less than 2500 grams. Childhood disease was defined as any illness, impairment, or abnormal condition from 4 weeks after birth up to 3 years of age.[11] Radical hysterectomy was defined according to the 2017 Querleu-Morrow classification.[12]

A univariate analysis was performed. Categorical variables were expressed in absolute numbers or frequencies and percentage. Normal distribution was verified for continuous variables by the Shapiro-Wilk test. The data were then expressed as mean and SD or median and IQR. Analysis was performed in the statistical software R Project version 3.6.2. This project was approved by all local institutional review boards.

RESULTS

A total of 33 patients were included in the analysis. Median age was 34 years (range 31–36). Twenty (60.6%) patients were diagnosed at early stage (IB1=12, IB2=8), and 13 (39.4%) patients had locally advanced disease (IIA2=4, IIB=6, and IIIB=3). Cervical cancer was diagnosed in 11 (33.3%), 20 (60.6%), and 2 (6.1%) patients, in the first, second, and third trimester of pregnancy, respectively. Regarding histology, 30 patients (90.9%) had squamous cell tumor, 2 (6.1%) adenosquamous, and 1 (3.0%) adenocarcinoma. The median tumor size (measured clinically) was 4 cm (range 3–6). The most frequently used imaging modality was MRI in 19 patients (57.6%), followed by abdominal ultrasound in nine patients (27.3%), and a combination of abdominal ultrasound and MRI in three patients (9.1%). Information on imaging was not available for two patients (6.1%) (Table 1).

The median gestational age at start of chemotherapy was 21 weeks (range 18–27). Although 11 patients were diagnosed with cervical cancer in the first trimester, chemotherapy was not started during this time because it was considered contraindicated due to embryo organogenesis. The combination of carboplatin/paclitaxel was the most commonly used in 20 patients (60.6%), followed by cisplatin and paclitaxel in 7 (21.2%), cisplatin alone in 3 (9.1%). Cisplatin and 5-fluorouracil, gemcitabine and carboplatin, and carboplatin as single agent, were used in one patient (3.0%), each. The median number of cycles was 3 (range 2–4). Regarding maternal acute toxicity, 6 (18.2%) patients had the following toxicities: hematological 4 (12.1%), gastrointestinal 1 (3.0%), and peripheral neuropathy 1 (3.0%). No grade 3 toxicity was reported. Treatment was not suspended due to toxicity in any patient. Chemotherapy treatment ended at a median of 30 weeks (range 29–32). Data on imaging response to chemotherapy were reported for 25 patients: stable disease in 12 (36.4%) patients, partial response in 9 (27.3%) patients, complete response in 3 (9.1%) patients, and progression in 1 (3%) patient (Table 1). The patient with disease progression was diagnosed with a stage IIB, and received four cycles of neoadjuvant chemotherapy with cisplatin alone from week 19 to week 32.

Median gestational age at delivery was 35 weeks (range 34–36). Obstetric pathology was documented in seven patients: three patients (9.1%) had pre-term labor, three patients (9.1%) had intrauterine growth restriction, and one patient (3.0%) had a placenta percreta. All patients were delivered by cesarean section and had live births. Neonatal information was obtained for 24 patients. Median birth weight was 2340 g (range 2140–2640), and median birth length was 45.5 cm (range 43.8–47.0). Two (6.1%) neonates had low birth weight. In 15 patients, information from early childhood was obtained. With a median follow-up of 26 months (range 12–36), no pathologies were reported in childhood (Table 2).

Standard concurrent chemo-radiation was performed in 19 (57.6%) patients, radical hysterectomy in 11 (33.3%) patients, abandoned radical hysterectomy with para-aortic lymphadenectomy and ovarian transposition in 1 patient (3%), and no further treatment in 2 (6.1%) patients. Reasons for no further treatment

Table 1 Clinical characteristics and neoadjuvant chemotherapy

Characteristics	Patients (N=33) (%)
Clinical characteristics	
Age (years)	34 (31–36)*
FIGO stage	
Early (IB)	20 (60.6)
Locally advanced (IIA–IIIB)	13 (39.4)
Histology	
Squamous	30 (90.9)
Adenocarcinoma	1 (3.0)
Adenosquamous	2 (6.1)
Clinical tumor size (cm)	4 (3–6)*
Gestational age (weeks)	21 (13–24)*
Gestational age (trimester)	
First	11 (33.3)
Second	20 (60.6)
Third	2 (6.1)
Image	
MRI	19 (57.6)
AU	9 (27.3)
AU and MRI	3 (9.1)
Missing	2 (6.1)
Neoadjuvant treatment	
Chemotherapy agent	
Carboplatin and paclitaxel	20 (60.6)
Cisplatin and paclitaxel	7 (21.2)
Cisplatin	3 (9.1)
Cisplatin and 5-fluorouracil	1 (3.0)
Gemcitabine and carboplatin	1 (3.0)
Carboplatin	1 (3.0)
Number of cycles	3 (2–4)*
Gestational age to first cycle (weeks)	21 (18–27)*
Gestational age to last cycle (weeks)	30 (29–32)*
Toxicity	
Yes	6 (18.2)
No	26 (78.8)
Missing	1 (3.0)
Imaging response to neoadjuvant chemotherapy	
Stable	12 (36.4)
Partial	9 (27.3)
Complete	3 (9.1)
Progression	1 (3.0)
Missing	8 (24.2)

*Median (IQR).
AU, abdominal ultrasound; MRI, magnetic resonance Imaging.

were: one patient with locally advanced disease refused chemoradiation, had disease progression, and died 2 months after delivery. The second patient, diagnosed with early stage cancer, did not accept additional treatment after delivery and was lost to follow-up (Table 3). In five patients (45.4%) a cesarean section and type C1 radical hysterectomy was performed. Radical hysterectomy was postponed in six (54.5%) patients; surgery was performed at a median of 8 weeks (range 6–15) after delivery.

Table 2 Obstetric, perinatal, neonatal, and early childhood outcomes

Characteristics	Patients (N= 33 (%))
Obstetric and perinatal outcomes	
Obstetric disease	
Yes	4 (12.1)
No	23 (69.7)
Missing	6 (18.2)
Gestational age at delivery (weeks)	35 (34–36)*
Delivery	
Cesarean section	33 (100.0)
Vaginal delivery	0 (0.0)
Neonatal outcomes (n=24)	
Weight (g)	2340 (2140-2640)*
Height (cm)	45.5 (43.8–47.0)*
Apgar 1 min	8 (7–9)*
Apgar 5 minute	9 (8–10)*
Neonatal disease	
Yes	5 (20.8)
No	19 (79.2)
Childhood outcomes (n=15)	
Childhood disease	
Yes	0 (0.0)
No	15 (100.0)
Follow-up (months)	26 (12–36)*

*Median (IQR).

Data for oncological outcomes from 30 patients were recorded. Recurrence rate was 26.7% (n=8). The median time to recurrence was 16.9 months (range 10.4–25.4). A total of 75% (n=6) of recurrences occurred in patients with initial diagnosis of locally advanced cervical cancer. Online supplemental table S1 describes the patterns of recurrence and death in this population. After a median follow-up of 16.3 months (range 2.0–36.9), 23 (76.7%) patients were alive without disease, 3 (10%) patients were alive with disease and 4 (13.3%) patients had died. Three patients (9.1%) were lost to follow-up.

DISCUSSION

We found that the majority of patients undergoing neoadjuvant chemotherapy during pregnancy were diagnosed at early stage, in the second trimester, and with squamous histology. To our knowledge, there are fewer than 100 reported cases of neoadjuvant chemotherapy during pregnancy in patients with cervical cancer (Table 4).

Table 3 Definitive management and oncological outcomes

Characteristics	Patients (N=33 (%))
Definitive treatment	
Type of treatment	
Radical hysterectomy	11 (33.3)
Chemotherapy and radiotherapy	19 (57.6)
Other*	1 (3.0)
None	2 (6.1)
Timing of radical hysterectomy (n=12)	
Intrapartum	6 (50.0)
Postponed	6 (50.0)
Timing of postpartum radical hysterectomy (weeks)	8 (6–15)
Adjuvant treatment (n=12)	
Yes	3 (25.0)
No	9 (75.0)
Oncological outcomes (n=30)	
Follow-up (months)	16.3 (2.0–36.9)†
Recurrence	
Yes	8 (26.7)
No	22 (73.3)
Death	
Yes	4 (13.3)
No	26 (86.7)
Vital status to follow-up	
Alive without disease	23 (76.7)
Alive with disease	3 (10.0)
Died of disease	4 (13.3)

*In one case radical hysterectomy was then abandoned, and a para-aortic lymphadenectomy and ovarian transposition were done.
†Median (range).

It has been shown that oncological prognosis of cervical cancer during pregnancy is not worse than in non-pregnant women.[13 14] This was corroborated by Halaska et al, in a matched cohort study, including 132 patients and 256 controls from six European cancer centers; after matching for FIGO stage, and considering five different forms of treatment (primary surgical treatment, neoadjuvant chemotherapy, treatment delayed until delivery, intentional preterm delivery and immediate pregnancy termination), the authors found that the unadjusted HR of pregnancy for progression-free survival was 1.18 (95% CI 0.74 to 1.88). The authors concluded that the oncological prognosis of cervical cancer in pregnant patients is similar to that of non-pregnant patients.[5]

Platinum compounds are the most effective chemotherapy agents when treating non-pregnant patients with cervical cancer,[15 16] and the same activity profile has been described in pregnant patients.[17] In addition, combination schemas are more effective than single platinum administration.[2] In a systematic literature review of neoadjuvant platinum-based chemotherapy during the second and third trimester of pregnancy in women with cervical cancer that included 88 patients from 39 studies,[6] the authors found that 86 patients received cisplatin and just two received carboplatin-based combinations. Interestingly, Halaska et al[5] reported single agent cisplatin in 59.1% of patients, while combination chemotherapy was used in 40.9% (cisplatin with paclitaxel, cisplatin with vinorelbine, cisplatin with ifosfamide, and paclitaxel or carboplatin with paclitaxel). In our study, 66.7% of patients received carboplatin-based combinations compared with 33.3% of patients who received cisplatin-based regimens.

For the associated maternal chemotherapy toxicity, in the study by Song et al,[6] the authors reported moderate toxicity, including drug intolerance, thrombocytopenia, anemia, allergic reaction, neutropenia, nausea, and vomiting in 10 of 51 patients. This toxicity profile is similar to that found in our study.

Chemotherapy administration during the first trimester of pregnancy is contraindicated due to its association with spontaneous abortion, fetal death, and fetal malformations,;however, beyond the first trimester it appears a safe option to achieve fetal lung maturation.[18] Köhler et al published data on 21 patients with cervical cancer diagnosed during second trimester of pregnancy, in whom synchronous samples from maternal blood, umbilical cord blood, and amniotic fluid were taken and analyzed for platinum concentrations at the time of cesarean section. Platinum concentrations in umbilical cord blood and in amniotic fluid were 23–65% and 11–42% of the maternal blood concentrations, respectively.[19]

Potential toxicity from a platinum compound administered during the last two trimesters of pregnancy includes intra-uterine growth restriction, prematurity, and low birth weight in up to 50% of infants.[20] In the aforementioned systematic review,[6] the authors described no anomalies in 71 (81%) of 88 neonates, but 17 newborns exhibited several conditions, such as respiratory syndrome disorder (8 of 88), mild elevation in serum creatinine (1 of 88), anemia (1 of 88), first-degree intraventricular hemorrhage (1 of 88), severe bilateral perceptive hearing loss (1 of 88), respiratory syndrome disorder combined with hypotension (1 of 88), hypoglycemia (1 of 88), anemia (1 of 88), supraventricular tachycardia (1 of 88), and erythema (1 of 88). Another study that evaluated the neonatal outcome of 95 fetuses exposed to chemotherapy during pregnancy, showed that 25% were small for gestational age.[21] Finally, in a review of 1170 patients, with the longest date of neonatal oncological outcomes, a close relationship between platinum derivatives and small for gestational age infants was demonstrated (OR 3.12, 95% CI 1.45 to 6.70).[22]

Among the strengths of our study, we consider this is the largest series reported in literature, and its reflects the experience of specialized Latin American cancer institutions. Additionally, we had a relatively small loss of patients at follow-up (9%). Among the weaknesses, we recognize its retrospective design, always a likely source of biased information, the lack of a homogeneous chemotherapy regimen among institutions, possible missing information on maternal toxicity reports, the inclusion of early and advanced stages, and a short median follow-up time. There might also have been under-reporting information on neurodevelopment of newborns, and the potential late toxicity produced by in utero exposure to chemotherapy.

In this multicenter retrospective study of patients diagnosed with cervical cancer during pregnancy we found that neo-adjuvant chemotherapy is a feasible alternative to achieve fetal viability, with

Table 4 Case reports and series (≤5 patients) receiving neoadjuvant chemotherapy during pregnancy in patients with cervical cancer

Author	Year	Stage*	Chemotherapy	Response to chemotherapy	Treatment	Follow-up (months)	Status at last visit	Newborn
Giacolone	1996	IB1	Cisplatin	CR	CS RH PLND PALND	12	NED	Well
Lai	1997	IB2 (n=2)	Cisplatin, vincristine	SD; PR	CS RH (n=2)	52; 59	DOD, DOD	Well
Tewari	1998	IB2	Cisplatin, vincristine	PR	CS RH PLND	24	NED	Well
Tewari	1998	IIA	Cisplatin, vincristine	PR	CS RH PLND	5	DOD	Well
Marana	2001	IIB	Cisplatin, bleomycin	Declined treatment after delivery	CS	13	DOD	Well
Caluwaerts	2006	IB1	Cisplatin	PR	CS RH PLND PALND	10	NED	Well
Karam	2007	IB2	Cisplatin	PR	CS RH PLND PALND	14	NED	Well
Bader	2007	IIA	Cisplatin, vincristine	PR	CS RH PLND	80	NED	Well
Palaia	2007	IIB	Cisplatin, paclitaxel	PR	RH PLND	10	NED	Well
Benhaim	2008	IIIB	Vincristine	PD	CT XRT	10	DOD	Well
Boyd	2009	IIB	Cisplatin	NA	XRT	15	NED	Well
Seamon	2009	IIIB	Cisplatin, vincristine	PR	XRT	48	NED	Well
Abellar	2009	NA (n=2)	Cisplatin; cisplatin, 5 FU	NA; NA	NA, NA	NA	NA	Well
Chun	2010	IB1	Cisplatin, paclitaxel	PR	CS RH PLND PALND	49	DOD	Well
Favero	2010	IB1 (n=5)	Cisplatin	NA	NA	12 (n=3); 10; 5	NED (n=3) NED (n=2)	NA
Smyth	2010	IB2	Adriamycin, cyclophosphamide	PR	CS	NA	NED	Well
Chun	2010	IB2	Cisplatin, paclitaxel	PR	CS RH PLND PALND	60	NED	Well
Rabaiotti	2010	IB2	Cisplatin	SD	CS XRT	24	DOD	Well
Chun	2010	IIA	Carboplatin, paclitaxel	PR	CS RH PLND PALND	48	AWD	Well
Li	2011	IB2 (n=2)	Cisplatin, paclitaxel	PR	CS, XRT CS	21; 13	NED (n=2)	Well (n=2)
Fruscio	2012	IB1 (n=4)	Cisplatin	PR (n=3) SD (n=1)	CS RH	41; 65	NED (n=4)	Well
Fruscio	2012	IB2 (n=5)	Cisplatin, vincristine; cisplatin (n=3); cisplatin, paclitaxel	PR (n=3) SD (n=2);	CS RH XRT; CS RH; CS RH; CS RH XRT	21; 13; 27; 153;113.	NED (n=4); DOD (n=1)	Well (n=5)
Yousefi	2012	IB2	Cisplatin, paclitaxel	CR	CS RH PLND PALND	6	NED	Well
Ayhan	2012	IB1	Cisplatin	SD	CS RH PLND	36	NED	Well
de Lima	2013	IB1	Cisplatin, vincristine	PR	CS RH PLND CT	24	NED	Well
Dawood	2013	IIB	Cisplatin	SD	CS XRT	24	DOD	Well
Kong	2014	IB1 (n=2)	Cisplatin, paclitaxel	PR	CS RH PLND CT	104; 24	NED	Well
Kong	2014	IB2	Cisplatin, paclitaxel	PR	CS RH PLND CT	35	NED	Well
Peculis	2015	IB2	Cisplatin, adriamycin	CR	CS RH PLND	20	NED	Well
Zhang	2015	IB1 (n=1) IIA (n=1)	Bleomycin, ifosfamide, cisplatin; cisplatin, paclitaxel	PR	CS RH PLND XRT; CS RH PLN CT	13; 68	NED; DOD	Well (n=2)
Ricci	2016	IB2 (n=2) IIA(n=2)	Cisplatin (n=2); paclitaxel (n=2)	PR (n=3) CR (n=1)	CS RH PLND XRT (n=3); CS RH PLND (n=1)	19 (n=1); 31 (n=2) 36 (n=1)	DOD (n=1), NED (n=3)	Well

Continued

Table 4 Continued

Author	Year	Stage*	Chemotherapy	Response to chemotherapy	Treatment	Follow-up (months)	Status at last visit	Newborn
Hecking	2016	IB1	Cisplatin	CR	CS RH PLND XRT	18	NED	Well
Vincenzo	2018	IB2	Cisplatin, paclitaxel	PR	CS RH PLND PALND XRT	22	NED	AML
Guo	2020	IB3	Carboplatin, paclitaxel	PR	CS RH PLND XRT	4	NED	Well
Wong	2020	IIIB	Carboplatin, paclitaxel	PR	CS XRT	6	DOD	Well

*All stages correspond to FIGO 2009 cervical cancer stage with the exception of Guo 2020.
AML, acute myeloid leukemia developed 22 months after exposure; AWD, alive with disease; CR, complete response; CS, cesarean section; CT, chemotherapy; DOD, death of disease; NA, not available; NED, no evidence of disease; PALND, pelvic-aortic lymphadenectomy; PD, progressive disease; PLND, pelvic lymphadenectomy; PR, partial response; RH, radical hysterectomy; SD, stable disease; XRT, radiotherapy.

low associated toxicity and favorable obstetric-neonatal outcomes. In early stage, we consider that radical surgery is feasible at the time of cesarean section or 8 weeks later, without affecting the oncological outcome of these patients. However, a quarter of patients had recurrent disease, and of these, 75% had been diagnosed with locally advanced stages of cancer, suggesting that the oncologic prognosis seems to be related to the initial stage of the disease, as occurs with non-pregnant patients.

Multicenter collaborative efforts are needed to collect information on pregnant patients with cervical cancer, in order to offer an adequate therapeutic strategy, that provides a balance of maternal survival and fetal/neonatal well-being.

Author affiliations
[1]Department of Gynecologic Surgery, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru
[2]Department of Gynecology Oncology, Instituto Nacional de Cancerologia, Bogota, Colombia
[3]Department of Gynecology and Obstetrics. Section of Gynecologic Oncology, Fundacion Santa Fe de Bogota, Bogota, Colombia
[4]Department of Gynecology and Obstetrics, Hospital General San Juan de Dios, Guatemala City, Guatemala, Guatemala
[5]Hospital Municipal de Oncologia Marie Curie, Buenos Aires, Federal District, Argentina
[6]Instituto Regional de Enfermedades Neoplásicas (IREN Sur), Arequipa, Peru
[7]Hospital Nacional Cayetano Heredia, Lima, Lima, Peru
[8]Hospital de Câncer de Barretos, Barretos, São Paulo, Brazil
[9]Unidad de Terapia Antineoplásica (UTAN), Centro Médico Guerra Méndez, Valencia, Venezuela, Bolivarian Republic
[10]Department of Gynecologic Oncology, Instituto de Cancerología- Las Américas-AUNA, Medellin, Antioquia, Colombia
[11]Department of Gynecologic Oncology, Hospital Militar Centra, Bogotá, Colombia
[12]Department of Gynecologic Oncology, Hospital Pereira Rossell, Montevideo, Uruguay
[13]Department of Gynecology, Hospital de Clínicas Dr. Manuel Quintela, Universidad de la República, Montevideo, Uruguay
[14]Servicio Oncológico Hospitalario del Instituto Venezolano de los Seguros Sociales, Caracas, Venezuela
[15]Clínica de Oncología Astorga, Universidad Pontificia Bolivariana, Medellin, Colombia

Twitter Erick Estrada @mderickestrada, Alfredo Borges Garnica @oncologiahoy and Jorge Hoegl @oncohoegl

Contributors AL, JR, RP designed the manuscript. AL, JR, RP, AAr, CC, KA, CDP, AB, GJRP, AAI,OS, SS, JL, DG, FT, JH, FC contributed with cases and checked the databases. EEE, JR analyzed the data. AL, JR, RP, EEE wrote the manuscript. All authors reviewed the manuscript and approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Juliana Rodriguez http://orcid.org/0000-0002-5472-4093
Gabriel Rendón http://orcid.org/0000-0002-7536-0567
Adriana Alméciga http://orcid.org/0000-0001-9154-4502
René Pareja http://orcid.org/0000-0003-0093-0438

REFERENCES

1 The Catalan Institute of Oncology (ICO) and the International Agency for Research on Cancer (IARC). Available: https://www.hpvcentre.net/datastatistics.php [Accessed 16 Aug 2020].
2 Amant F, Halaska MJ, Fumagalli M, *et al*. Gynecologic cancers in pregnancy: guidelines of a second international consensus meeting. *Int J Gynecol Cancer* 2014;24:394–403.
3 Boere I, Lok C, Vandenbroucke T, *et al*. Cancer in pregnancy: safety and efficacy of systemic therapies. *Curr Opin Oncol* 2017;29:328–34.
4 Amant F, Berveiller P, Boere IA, *et al*. Gynecologic cancers in pregnancy: guidelines based on a third International consensus meeting. *Ann Oncol* 2019;30:1601–12.
5 Halaska MJ, Uzan C, Han SN, *et al*. Characteristics of patients with cervical cancer during pregnancy: a multicenter matched cohort study. An initiative from the International network on cancer, infertility and pregnancy. *Int J Gynecol Cancer* 2019:676–82.
6 Song Y, Liu Y, Lin M, *et al*. Efficacy of neoadjuvant platinum-based chemotherapy during the second and third trimester of pregnancy in women with cervical cancer: an updated systematic review and meta-analysis. *Drug Des Devel Ther* 2019;13:79–102.
7 Schwartz LH, Litière S, de Vries E, *et al*. RECIST 1.1-Update and clarification: from the RECIST Committee. *Eur J Cancer* 2016;62:132–7.

8 American College of Obstetricians and Gynecologists. ACOG practice bulletin No. 134: fetal growth restriction. *Obstet Gynecol* 2013;121:1122–33.
9 Royal College of Obstetricians and Gynaecologists. Small-For-Gestational-Age fetus, investigation and management (Green-top guideline No. 31). Available: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf [Accessed 16 Aug 2020].
10 Hughes MM, Black RE, Katz J. 2500-g low birth weight cutoff: history and implications for future research and policy. *Matern Child Health J* 2017;21:283–9.
11 Mokkink LB, van der Lee JH, Grootenhuis MA, *et al*. Defining chronic diseases and health conditions in childhood (0-18 years of age): National consensus in the Netherlands. *Eur J Pediatr* 2008;167:1441–7.
12 Querleu D, Cibula D, Abu-Rustum NR. 2017 update on the Querleu-Morrow classification of radical hysterectomy. *Ann Surg Oncol* 2017;24:3406–12.
13 Lee J-M, Lee K-B, Kim Y-T, *et al*. Cervical cancer associated with pregnancy: results of a multicenter retrospective Korean study (KGOG-1006). *Am J Obstet Gynecol* 2008;198:92.e1–6.
14 Bigelow CA, Horowitz NS, Goodman A, *et al*. Management and outcome of cervical cancer diagnosed in pregnancy. *Am J Obstet Gynecol* 2017;216:276.e1–6.
15 Friedlander M, Kaye SB, Sullivan A, *et al*. Cervical carcinoma: a drug-responsive tumor--experience with combined cisplatin, vinblastine, and bleomycin therapy. *Gynecol Oncol* 1983;16:275–81.
16 Rydzewska L, Tierney J, Vale CL, *et al*. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. *Cochrane Database Syst Rev* 2012;12.
17 Zagouri F, Sergentanis TN, Chrysikos D, *et al*. Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis. *Obstet Gynecol* 2013;121:337–43.
18 Peccatori FA, Azim HA, Orecchia R, *et al*. Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl 6):vi160–70.
19 Köhler C, Oppelt P, Favero G, *et al*. How much platinum passes the placental barrier? AnalysisA of platinum applications in 21 patients with cervical cancer during pregnancy. *Am J Obstet Gynecol* 2015;213:206.e1–5.
20 Brewer M, Kueck A, Runowicz CD. Chemotherapy in pregnancy. *Clin Obstet Gynecol* 2011;54:602–18.
21 de Haan J, Verheecke M, Van Calsteren K, *et al*. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol* 2018;19:337–46.
22 Amant F, Vandenbroucke T, Verheecke M, *et al*. Pediatric outcome after maternal cancer diagnosed during pregnancy. *N Engl J Med* 2015;373:1824–34.