original report

Cervical Cancer Treatment Delays and Associated Factors in a Cohort of Women From a Developing Country

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abstract

PURPOSE To estimate treatment delays and associated factors among women diagnosed with cervical cancer who were treated at the main cancer center in Rio de Janeiro, Brazil.

MATERIALS AND METHODS A retrospective cohort study was performed comprising 865 women newly diagnosed with cervical cancer between 2012 and 2014. Times from diagnosis to treatment initiation (less than or equal to 60 days) and from diagnosis to treatment ending (less than or equal to 120 days) were analyzed according to the Brazilian law for the treatment of patients with cancer. Associations between treatment delays and sociodemographic, economic, lifestyle, clinical, and treatment variables were estimated using logistic regression models, with 95% CIs.

RESULTS The average age was 48 (± 13.7) years, and the median age was 47 years; 36.2% of patients had stage IIIB to IVA disease. The median time from diagnosis to treatment initiation was 114 days, which was statistically higher among women with stage IIB to IVA (105.5 days) compared with those with earlier stages (119 days). The delay in treatment initiation occurred in 92.8% of participants; the median time from diagnosis to treatment ending was 274 days, with a delay (more than 120 days) for 92.6% of patients. The median time interval from diagnosis to the first visit to the cancer center was 28 days, with a delay of more than 30 days for 46.6% of patients. Age (odds ratio [OR], 1.05; 95% CI,1.02 to 1.08), stage IIIB to IVA (OR, 0.38; 95% CI, 0.16 to 0.90), time to first visit to the cancer center (OR, 11.52; 95% CI, 4.32 to 30.66), chemoradiation treatment (OR, 4.56; 95% CI, 1.81 to 11.47), and adequate treatment (OR, 2.57; 95% CI, 1.26 to -5.40) were independently associated with delay of treatment initiation.

CONCLUSION Significant delays in treatment initiation and ending were observed in this studied population. The treatment initiation delay was positively associated with age, time interval more than 30 days from diagnosis to first specialist assessment at the cancer center, treatment with chemoradiation, and adequate treatment.

INTRODUCTION

Cervical cancer is an important public health problem worldwide, especially in developing countries, where it is the second most common cancer among women.[1] Developed countries with broad-coverage Papanicolaou-test screening programs have experienced a decline in cervical cancer incidence and mortality over the past decades.[2] However, in developing countries, cervical cancer incidence and mortality rates are still considered high, and survival is poor.[1,3-8] Such rates could be attributed to late organization of screening programs, low access to the health care system, low education level of the population at risk, and delays in diagnosis and treatment of this neoplasia.[2,5,8-12]

Cervical cancer treatment is usually either chemoradiation or radical hysterectomy/trachelectomy with lymph node dissection in early stages and chemoradiation in advanced stages. Depending on the patient's health status, such as age, comorbidity, and disease presentation, the treatment may be adjusted accordingly.[13] Delays in diagnosis and treatment initiation and/or conclusion are experienced by patients with cervical cancer regardless of the country and/or institution they are being treated.[9,14,15] Long waiting times for surgery or radiation are usually associated with poor access to services, poor quality of health care,[14-18] and request for a second opinion or time-consuming pathologist reviews that might affect treatment.[16] Delays can also be due to patient factors, such as sociodemographic factors, comorbidities, social influences, and previous experiences.[19,20]

According to international standards for early cancer diagnosis and treatment, the time intervals that should

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be measured include appraisal (interval from bodily changes and patient appraisal and self-management); help-seeking (time to decide to consult a hospital cancer physician/practitioner and arrange an appointment); diagnostic (interval between first consultation with a health care practitioner and diagnosis); and pretreatment (time interval from diagnosis to start of treatment).[20-22] Regarding cervical cancer, time intervals from diagnosis to treatment initiation and completion are also important to guarantee treatment efficacy and improve survival.[9,12,14,23] Evidence supports that a waiting time of more than 60 days from cancer diagnosis to treatment initiation could lead to poorer survival compared with women who start treatment within 60 days after diagnosis.[24] The National Breast and Cervical Cancer Early Detection and Treatment Program indicator of timely follow-up (National Comprehensive Cancer Network) postulated that severe therapeutic care delay was defined as a delay of 60 days or more from final cervical cancer diagnosis to the initiation of treatment.[25] Also, a delay of cancer therapeutic care greater than 3 months could harm prognosis, increase morbidity, reduce survival, and jeopardize survivorship.[26,27] However, some studies did not find statistical significance on delays to treatment and survival rates among women with cervical cancer in the United States.[12,23] Such controversy could be due to delay-to-treatment definitions, study population base (hospital based *v* population based), sample size, stage at diagnosis, treatment protocols, and time interval from treatment initiation to conclusion.[25,28]

Brazilian public health care is universal and covers approximately 70% of cervical cancer treatment in the country.[29] The Brazilian government issued a law in 2012 determining that every patient with cancer should start the treatment within 60 days from the date that diagnosis is histologically confirmed, aiming to guarantee the same treatment access to every user of the public health system.[30] In 2013, another law was issued establishing that the counting of the time to treatment initiation should begin with the date that the diagnosis was registered on the medical report.[31] To our knowledge, there is no study in Brazil evaluating the delays in cervical cancer treatment on the basis of international criteria. This study aimed to estimate treatment delays and associated factors among patients with cervical cancer referred to the Gynecologic Cancer Hospital of National Cancer Institute in Brazil (HC-II/NCI).

MATERIALS AND METHODS

Study Design and Participants

A retrospective study was performed in a cohort of women diagnosed with cervical cancer and referred to the HC-II/NCI in Rio de Janeiro. In 2010, the cancer care access regulation system was established in the city of Rio de Janeiro, creating a list of patients diagnosed with cancer and referring them to a cancer treatment center.[32] Although the cancer treatment centers could still receive patients with cancer on the basis of free demand and/or who were referred by a private doctor or health care professional familiar with the institutional flow,[32] a few women in the sample (n = 46) did not follow the regular flow of the public health care service.

All women newly diagnosed with cervical cancer (International Classification of Diseases code 10:C.53) from July, 1, 2012, to October, 31, 2014, were eligible. The inclusion criteria were all consecutive patients with a histologically confirmed diagnosis of cervical cancer (encompassing adenocarcinoma, squamous carcinoma, and adenosquamous carcinoma) who were completely treated at HC-II/NCI. Patients were identified and selected using the Hospital Cancer Registry (HCR/HC-II) database, and the registered diagnosis was cross-tabled with histopathologic reports. From 2012 to 2014, 1,483 women registered as C.53 (International Classification of Diseases code 10) in the HCR/HC-II database. Of these, 489 patients (33%) were excluded: 23 were treated at another cancer center, nine had a histologic result other than epithelial, 40 had a second primary cancer site, 140 received only brachytherapy at HC-II/NCI, and 201 had precancerous lesions on the histologic report; patients classified as stage IVB (n = 76) were excluded from the analysis because treatment at this stage is for symptomatic relief rather than curative purposes. Of 994 eligible patients, 204 (20.5%) were lost to follow-up: 45 because medical files were not found, and 159 had no treatment information. Thus, the studied population included 790 patients with cervical cancer (Fig 1). This study was approved by the Research Ethics Board at the National School of Public Health in Brazil.

Variables

Two trained nurses extracted all studied data from electronic and physical medical reports. Outcomes were set as three waiting times (Fig 2): T1—days from diagnosis to first specialist assessment (FSA; including the referral to the cancer center, scheduling the FSA, personal appraisal of the FSA); T2—days from diagnosis to first treatment initiation (including T1+ staging, treatment definition, pre-radiotherapy referral, presurgical tests, surgery appraisal); T3—days from diagnosis to treatment conclusion (including T1+T2+ dates and types of surgery, chemoradiation and radiation only, dates of treatment completion). Delays-in-treatment definitions were based on the literature and on sample distributions as follows: 30 days or less versus 30 days or more (T1); 60 days or less versus 60 days or more (T2)[24,32]; to 120 days or less versus 120 days or more (T3).[24,25,32]

Independent variables included sociodemographic characteristics, such as age at diagnosis, place of residence (Rio de Janeiro *v* other city/state), ethnicity (white/non-white), education (no education *v* high school/college),

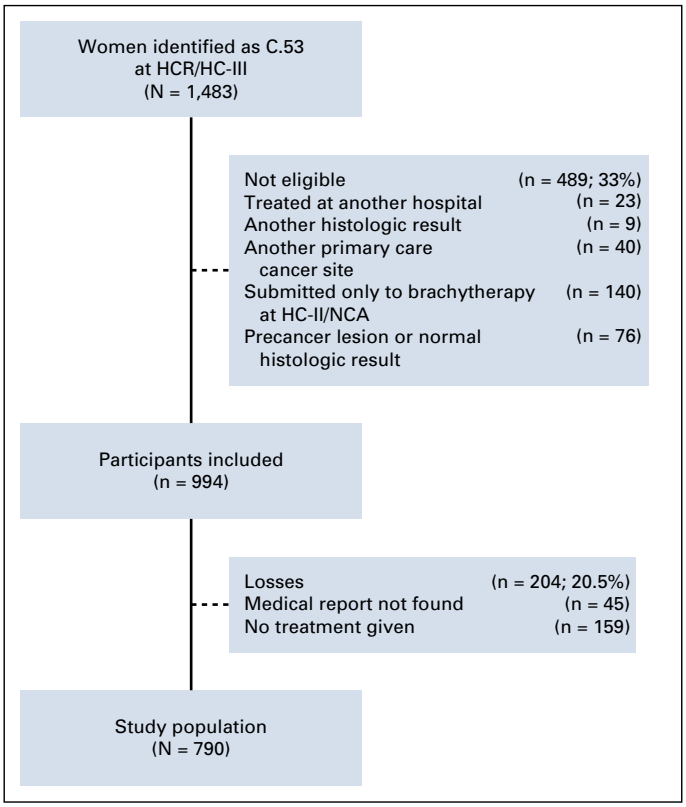

FIG 1. Eligibility flow of studied population. HCR/HC-II, Hospital Cancer Registry/Gynecologic Cancer Hospital.

occupation level (< high school *v* ≥ high school), and family income (family income twice the minimum wage or less *v* over twice the minimum wage; and clinical variables and habits, such as comorbidities (yes/no) and tobacco smoker (never/former/current).

Disease presentation and treatment were classified according to the International Federation of Gynecology and Obstetrics stage at diagnosis (I, II, III, and IV)[33] and then were grouped as local early stages/bulky (IA1 to IIA2), locally advanced (IIB to IIIA), and late stage (IIIB to IVA). Additional classifications included histopathologic results (squamous carcinoma *v* adenocarcinoma/adenosquamous carcinoma),[34] surgery (yes/no), external beam radiotherapy to the pelvis (yes/no), brachytherapy insertion (yes/no), and treatment protocol (surgery only/surgery plus chemoradiation/radiation only).[25,28] Following International Federation of Gynecology and Obstetrics recommendations,[35] treatment at stages IA2, IB, and IIA was either radical hysterectomy/radical trachelectomy with bilateral lymph node dissection or, alternatively, concurrent chemoradiation with a platinum-based regimen for radiosensitization. The latter treatment combination was administered to patients at stages IB2, IIB, III, and IVA. Adjuvant radiation was prescribed for patients who underwent radical hysterectomy/trachelectomy but were found postoperatively to have lymph node metastases, close or involved surgical margins, or parametrial involvement,[36] or had at least two of the following risk factors: deep stromal invasion, lymphovascular space invasion, or tumor diameter greater than 4 cm.[37] Thus, adequacy of treatment (yes/no) was established by combining the treatment protocol performed with the stage group.

Statistical Analysis

Descriptive analyses were performed through frequency distributions of categorical variables according to stage. Percentage differences were evaluated through χ^2 and Fisher tests, considering a significance level of 5%. Time intervals from histologic diagnosis and FSA to treatment initiation and to treatment completion were analyzed as

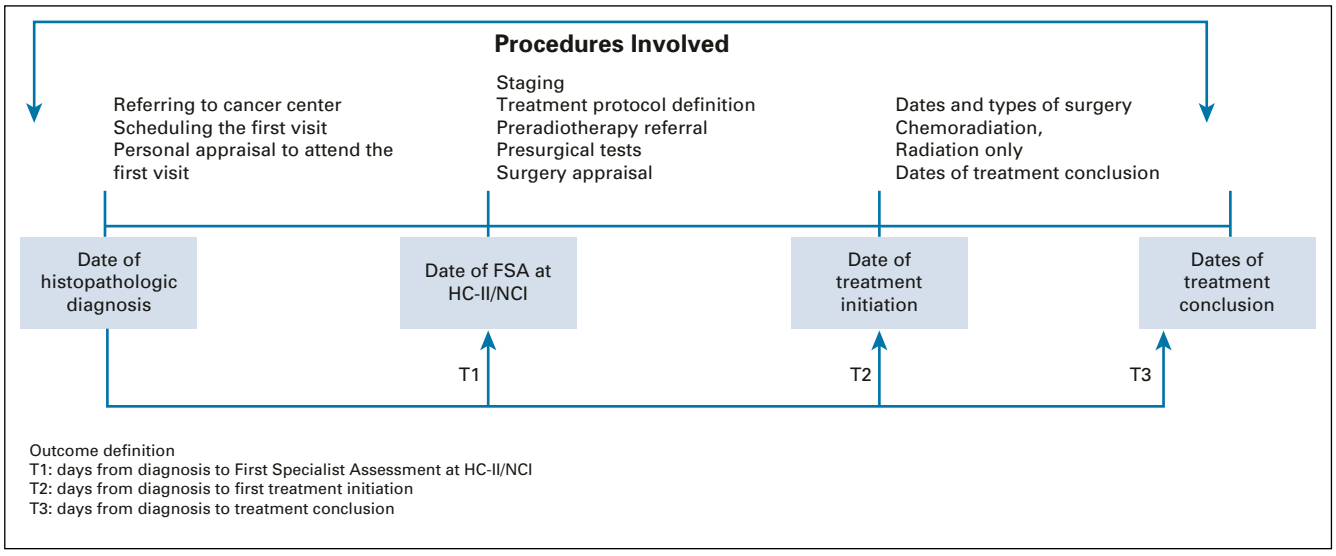

FIG 2. Cervical cancer care pathway and outcome definitions. T1, days from diagnosis to first specialist assessment (FSA) at Gynecologic Cancer Hospital of National Cancer Institute in Brazil (HC-II/NCI). T2, days from diagnosis to first treatment initiation. T3, days from diagnosis to treatment conclusion.

continuous and categorical variables. Median differences among time intervals, according to stage and treatment, were analyzed using the Kruskal-Wallis test and the Mann-Whitney *U* test, with a significance level of 5%.

Prevalence of initial treatment delays (greater than 60 days) for each covariable was categorized according to stage. Crude and stratified-by-stage odds ratios (ORs), with their respective 95% CIs, for treatment initiation delays were estimated using a nonconditional logistic regression model. Multiple logistic regressions were used to estimate adjusted ORs and 95% CIs using the Wald statistic test. Biologic relevance and statistical significance in crude analyses were the criteria to include the variables in the final model. A significance level of 5% was used to retain the variable in the model. Final model diagnosis was performed by means of a residual analysis, and the Hosmer-Lemeshow goodness-of-fit test. All analyses were performed using the SPSS statistical package (version 20.0; SPSS, Chicago, IL).

RESULTS

In this sample, 67.7% of patients presented for diagnosis at a late stage (a stage greater than IIB), 70.1% were older than 40 years of age, only 17.2% lived in Rio de Janeiro city, 67.5% were nonwhite, 71.8% had a low education level (less than elementary school), 63.4% had a family income of up to twice the minimum wage, and 74.3% received chemoradiation. Compared with women treated with surgery, those treated with chemoradiation were mainly older than 40 years of age (74.1%), had lower education levels (75.8%), and had a higher frequency of stage IIB or greater at diagnosis (85.8%). However, they also had a lower frequency of adenocarcinoma (13.6%), adequate treatment (58.1%), and less FSA delay (43.9%; Table 1).

The median time interval from diagnosis to FSA was 28 days, varying from 27 days among the radiotherapy group to 37 days among the surgery group and from 26.5 days in the stage IIIB to IVA group to 33 days in the stage IA1 to IIA2 group (Table 2). The median time from diagnosis to treatment initiation was 114 days, varying from 105 days among patients with stage IIIB to IVA disease to 119 days among patients with earlier stages. Only 7.2% of this population initiated treatment before 60 days, and 68.8% initiated it in more than 90 days. Only 4% of the women with stage IIB to IIIA disease were treated within 60 days, whereas approximately 8.5% of those with earlier and later stages were treated within this period (Table 2). The median time from diagnosis to treatment conclusion was 274.5 days, varying from 268 days for women treated with radiation to 357 days among those treated with surgery ($P < .001$). Considering the stage at diagnosis, the median time varied from 252 days among women at stage IIIB to IVA to 302 days among women at stage IA1 to IIA2 ($P < .001$). Only 7.4% completed treatment within 120 days, varying from 5.3% among the women treated with surgery to 7.6% among those treated with radiation. Overall, 75% completed the treatment in more than 200 days, whereas among those treated with surgery, 90.3% had a time interval of more than 200 days from diagnosis to treatment conclusion ($P = .003$). On the basis of the stage at diagnosis, only 0.9% of women with early-stage disease concluded treatment within 120 days, whereas 11.4% of patients with stage IIIB to IVA and 5.8% of patients with stage IIB to IIIA concluded in this period ($P = .001$). Also, 68.3% of later-stage patients (IIIB to IVA) and more than 80% of patients in earlier stages concluded treatment in more than 200 days (Table 2).

The prevalence of treatment initiation delays was more than 80% for all variables evaluated (Table 3). Overall, age older than 40 years (OR, 2.18; 95% CI, 1.26 to 3.77); nonwhite ethnicity (OR, 2.04; 95% CI, 1.18 to 3.52); receipt of external radiation (OR, 1.83; 95% CI, 1.00 to 3.34) or brachytherapy (OR, 3.15; 95% CI, 1.80 to 5.53); being included in the chemoradiation protocol (OR, 1.84; 95% CI, 1.04 to 3.24); and time from diagnosis to FSA (OR, 8.53; 95% CI, 3.34 to 21.76) were positively associated with treatment initiation delay. Occupation level ≥ high school (OR, 0.43; 95% CI, 0.24 to 0.75), family income more than twice the minimum wage (OR, 0.52; 95% CI, 0.28 to 1.00), and receiving surgery as the first treatment (OR, 0.55; 95% CI, 0.31 to 0.96) were negatively associated with treatment initiation delays. Women with stage IA1 to IIA2 disease, living in a city other than Rio de Janeiro (OR, 3.08; 95% CI, 1.24 to 7.70), who were nonwhite (OR, 3.45; 95% CI, 1.34 to 8.60), and with more than 30 days from diagnosis to FSA (OR, 11.45; 95% CI, 2.60 to 50.54) were positively associated with delays. Women with later stages of disease (IIIB to IVA), older than 40 years of age (OR, 2.92; 95% CI, 1.24 to 6.85), receiving brachytherapy (OR, 4.14; 95% CI, 1.74 to 10.00), receiving adequate treatment (OR, 4.00; 95% CI, 1.56 to 9.74), and with more than 30 days to FSA (OR, 5.00; 95% CI, 1.43 to 17.40) were statistically associated with treatment initiation delays.

In the multiple logistic regression (Table 4), delays were independently associated with age (OR, 1.05; 95% CI, 1.02 to 1.08), having later stage at diagnosis (OR, 0.38; 95% CI, 0.16 to 0.90), spending over 30 days from diagnosis to FSA (OR, 11.52; 95% CI, 4.32 to 30.66), receiving chemoradiation treatment (OR, 4.56; 95% CI, 1.81 to 11.47), and receiving adequate treatment protocol (OR, 2.57; 95% CI, 1.26 to 5.40).

DISCUSSION

To our knowledge, this study is the first one in Brazil to describe the clinical pathway for women with cervical cancer at stages IA1 to IVA. The overall median time from histopathologic diagnosis to first treatment initiation was 114 days, despite the type of treatment indicated, being slightly shorter among late-stage patients (105 days). This reality is potentially concerning, because less than 10% of the study population was treated within 60 days from

TABLE 1. Characteristic Distributions of a Cohort of Women Diagnosed With Cervical Cancer and Treated at National Cancer Institute, Rio de Janeiro, Brazil (2012 to 2014)

		Stage at Diagnosis			χ^2 Test
Characteristic	**Total Patients***	**Surgery Only**	**Surgery Plus Radiation**	**Chemoradiation**	***P***
Patients, No.	790 (100)	147 (18.6)	56 (0.1)	587 (74.3)	< .001
Age at diagnosis, years					< .001
< 40	236 (29.9)	66 (44.9)	24 (42.9)	146 (24.9)	
≥ 40	554 (70.1)	81 (55.1)	32 (57.1)	441 (74.1)	
Residency					.80
Rio de Janeiro	136 (17.2)	34 (23.1)	11 (19.6)	91 (15.5)	
Other cities/states	654 (82.8)	113 (76.9)	45 (80.4)	496 (84.5)	
Ethnicity					.138
White	257 (32.5)	59 (39.5)	17 (30.4)	182 (31.0)	
Nonwhite	533 (67.5)	89 (60.5)	39 (69.6)	405 (69.0)	
Education					< .001
≤ Middle school	567 (71.8)	85 (57.8)	37 (66.1)	445 (75.8)	
> Middle school	223 (28.2)	62 (42.0)	19 (33.9)	142 (24.2)	
Occupation level					<.001
< High school	558 (72.6)	83 (58.0)	36 (65.5)	439 (76.9)	
≥ High school	211 (27.4)	60 (42.0)	19 (34.5)	132 (23.1)	
Family income†					.041
≤ Twice the minimum wage	408 (63.4)	67 (54.0)	34 (70.8)	307 (65.0)	
> Twice the minimum wage	236 (36.6)	57 (46.0)	14 (29.2)	165 (35.0)	
Comorbidity					.241
No	125 (16.8)	18 (12.9)	06 (12.5)	101 (18.2)	
Yes	618 (83.2)	121 (87.1)	42 (87.5)	455 (81.8)	
Smoking					.266
Never	439 (55.8)	92 (62.6)	34 (60.7)	313 (53.6)	
Former	183 (23.3)	26 (17.7)	11 (19.6)	146 (25.0)	
Current	165 (21.0)	29 (19.7)	11 (19.6)	125 (21.4)	
Histology					< .001
Squamous cell carcinoma	638 (82.7)	102 (71.3)	40 (74.1)	496 (86.4)	
Adenocarcinoma	133 (17.3)	41 (28.7)	14 (25.9)	78 (13.6)	
Stage					< .001
IA1-IIA2	255 (32.3)	141 (95.9)	31 (55.4)	83 (14.1)	
IIB-IIIA	249 (31.5)	03 (2.0)	11 (19.6)	235 (40.0)	
IIIB-IVA	286 (36.2)	03 (2.0)	14 (25.0)	269 (45.8)	
Treatment adequacy					< .001
Inadequate	257 (32.5)	06 (4.1)	05 (8.9)	246 (41.9)	
Adequate	533 (67.5)	141 (95.9)	51 (91.1)	341 (58.1)	
Time to FSA					.027
≤ 30 days	408 (53.4)	63 (43.8)	28 (50.9)	317 (56.1)	
> 30 days	356 (46.6)	81 (56.3)	27 (49.1)	248 (43.9)	

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviation: FSA, first specialist assessment.

*Total may vary because of missing values.

†According to the minimum wage in the year of diagnosis.

TABLE 2. Time Interval Distribution Among Women Diagnosed With Cervical Cancer and Treated at National Cancer Institute in Rio De Janeiro, According to First Treatment and Stage at Diagnosis (2012 to 2014)

	First Treatment				Stage at Diagnosis			
	Days From Diagnosis to FSA				Days From Diagnosis to First Hospital Visit			
Estimate	**Total**	**Surgery***	**Radiotherapy**	***P***	**IA1-IIA2**	**IIB-IIIA**	**IIIB-IVA**	***P***
Mean (SD)	45.5 (58.7)	59.23 (72.15)	40.6 (52.4)	< .001†	56.31 (72.1)	41.81 (46.6)	38.9 (53.1)	< .001‡
Median	28	37	27		33	27	26.5	
Min-max	1-580	1-580	1-514		1-580	1-352	1-514	
≤ 30	408 (53.4)	91 (45.7)	317 (56.1)	< .001§	19 (47.8)	130 (54.9)	159 (57.2)	.006§
31-60	211 (27.6)	51 (26.5)	160 (28.3)		70 (28.1)	63 (26.6)	78 (28.1)	
> 60	145 (19.0)	57 (28.6)	88 (15.6)		60 (24.1)	44 (18.6)	41 (14.7)	
Days From Diagnosis to Begin Treatment					Days From Diagnosis to Begin Treatment			
Mean (SD)	137.8 (90.2)	149.6 (110.0)	133.8 (82.1)	.490†	150.5 (105.8)	140.9 (86.4)	123.9 (75.68)	.003‡
Median	114	115	113		119	119	105.5	
Min-max	8-873	21-873	8-873		21-873	34-873	8-513	
≤ 60	56 (7.2)	21 (10.6)	35 (6.0)	.100§	22 (8.8)	10 (4.0)	24 (8.5)	.052§
61-90	187 (24.0)	47 (23.6)	140 (24.1)		53 (21.1)	56 (22.7)	78 (27.7)	
> 90	537 (68.8)	131 (65.8)	406 (69.9)		176 (70.1)	181 (73.3)	180 (63.8)	
Days From Diagnosis to End Treatment					Days From Diagnosis to End Treatment			
Mean (SD)	284.2 (129.7)	383.2 (172.6)	274.5 (120.6)	< .001†	330.35 (154.8)	296 (122.7)	255.2 (117.2)	< .001‡
Median	274.5	357	268		302	284	252	
Min-max	40-1,157	68-1,157	40-911		68-1,157	60-911	40-736	
≤ 120	47 (7.4)	3 (5.3)	44 (7.6)	.003§	1 (0.9)	14 (5.8)	32 (11.4)	.001§
120-200	110 (17.2)	1 (1.8)	109 (18.8)		19 (16.5)	34 (14.0)	57 (20.3)	
> 200	481 (75.4)	53 (90.3)	428 (73.7)		95 (82.6)	194 (80.2)	192 (68.3)	

NOTE: Data are No. (%) unless otherwise indicated.

Abbreviations: FSA, first specialist assessment; max, maximum; min, minimum; SD, standard deviation.

*Surgery only or combined with radiation and/or chemotherapy.

†Mann-Whitney *U* test.

‡Kruskal-Wallis test.

§χ^2 test.

diagnosis, although it was mandatory by law. In addition, a major variation in the time to complete the pathway was observed among the stages, with the median time reaching more than 300 days among women treated with surgery and among those in early stages (IA1 to IIA2).

The FSA timing varied from 27 days among women first treated with radiation to 37 days among women first treated with surgery. Thus, an FSA more than 30 days was the strongest factor independently associated with increased risk of treatment initiation delay. Similar findings were observed in New Zealand among women from the private and public sectors, where the median time from referral to treatment initiation for all patients was 97 days. A shorter median time to FSA in the private sector was associated with a reduction in median duration of the overall pathway and was the only factor significantly associated with reduced times from referral to treatment initiation in the multivariable analysis.[38] Because our study was performed in the public sector only, our findings may reflect the patterns of health care use and the effectiveness of primary and secondary care services in Rio de Janeiro. Also, they may be a result of structural (geographic distance to the treatment facility and availability of transportation)[21] and nonstructural (individual patient and physician factors)[39,40] barriers. Although there is no specific recommendation regarding the acceptable waiting time from referral to FSA in Brazil, the United Kingdom National Health Service guidelines[41] recommend that patients with either symptomatic or smear evidence of disease should have an FSA within 14 to 21 days. Should this recommendation be followed in Brazil, there would still be from 39 to 46 days left to proceed to staging, decision to treat, presurgery test/preradiotherapy referral, and surgery appraisal, meeting the Brazilian law requirement of 60 days from diagnosis to treatment initiation.

Studies have been published[42-44] linking delays between diagnosis and the start of radiotherapy with adverse effects on cervical cancer treatment outcome.[4] Since 1993,

TABLE 3. Prevalence of Delays in Treatment Initiation and Associated Factors in a Cohort of Women Diagnosed With Cervical Cancer and Treated at National Cancer Institute, Rio de Janeiro, According to Stage at Diagnosis (2012 to 2014)

	All Stages		IA1-IIA2		IIB-IIIA		IIIB-IVA	
Characteristics	**Prevalence**	**OR (95% CI)**	**Prevalence**	**OR (95% CI)**	**Prevalence**	**OR (95% CI)**	**Prevalence**	**OR (95% CI)**
Age, years								
≤ 40	88.8	1	89.1	1	94.3	1	84.1	1
> 40	94.5	**2.18 (1.26 to 3.77)**	92.9	1.60 (0.66 to 3.86)	96.4	1.60 (0.40 to 6.42)	93.9	**2.92 (1.24 to 6.85)**
Residence								
Rio de Janeiro	91.5	1	82.4	1	100	1	94.3	1
Other cities/state	93.1	1.25 (0.625 to 2.48)	93.5	**3.08 (1.24 to 7.70)**	95.1	—	91.1	6.20 (0.14 to 2.76)
Ethnicity								
White	89.4	1	84.6	1	94.0	1	89.9	1
Nonwhite	94.5	**2.04 (1.18 to 3.52)**	95.0	**3.45 (1.34 to 8.60)**	96.9	2.00 (0.56 to 7.11)	92.1	1.32 (0.54 to 3.21)
Education								
≤ Middle school	94.6	1	96.0	1	96.9	1	91.8	1
> Middle school	88.2	0.42 (0.42 to 7.32)	84.3	**0.23 (0.85 to 0.60)**	92.7	0.41 (0.11 to 1.51)	90.5	0.85 (0.23 to 2.24)
Occupation level								
< High school	94.7	1	94.0	1	96.9	1	93.3	1
≥ High school	88.5	**0.43 (0.24 to 0.75)**	86.2	**0.40 (0.16 to 0.97)**	91.8	0.36 (0.09 to 1.34)	89.2	0.60 (0.23 to 1.54)
Family income								
≤ Twice the minimum wage	95.0	1	93.8	1	99.2	1	92.6	1
> Twice the minimum wage	91.0	**0.53 (0.28 to 1.00)**	89.9	0.60 (0.22 to 1.60)	92.4	**0.10 (0.01 to 0.83)**	90.9	0.80 (0.28 to 2.25)
Comorbidity								
No	92.7	1	85.7	1	96.9	1	94.7	1
Yes	92.8	1.00 (0.48 to 2.12)	92.1	1.94 (0.66 to 5.70)	95.6	0.70 (0.08 to 5.70)	90.8	0.55 (0.16 to 1.92)
Tobacco smoking								
Never/former	92.7	1	91.1	1	96.8	1	90.6	1
Current	93.8	1.20 (0.60 to 2.42)	91.7	1.07 (0.35 to 3.32)	93.0	0.43 (0.12 to 1.60)	96.4	2.81 (0.64 to 12.34)
Surgery								
No	94.0	1	95.2	1	95.7	1	92.0	1
Yes	89.4	**0.55 (0.31 to 0.96)**	89.3	0.42 (0.40 to 1.30)	100	—	82.4	0.40 (0.11 to 1.52)
External radiation								
No	89.1	1	89.2	1	90.0	1	85.7	1
Yes	93.8	**1.83 (1.00 to 3.34)**	93.8	1.82 (0.71 to 4.62)	96.2	2.81 (0.32 to 24.67)	91.3	1.83 (0.21 to 15.83)

(Continued on following page)

TABLE 3. Prevalence of Delays in Treatment Initiation and Associated Factors in a Cohort of Women Diagnosed With Cervical Cancer and Treated at National Cancer Institute, Rio de Janeiro, According to Stage at Diagnosis (2012 to 2014) (Continued)

	All Stages		IA1-IIA2		IIB-IIIA		IIIB-IVA	
Characteristics	**Prevalence**	**OR (95% CI)**	**Prevalence**	**OR (95% CI)**	**Prevalence**	**OR (95% CI)**	**Prevalence**	**OR (95% CI)**
Brachytherapy								
No	87.7	1	89.3	1	91.9	1	83.1	1
Yes	95.7	**3.15 (1.80 to 5.53)**	94.6	2.08 (0.74 to 5.85)	96.7	2.55 (6.30 to 10.33)	95.3	**4.14 (1.74 to 10.00)**
Treatment protocol								
Surgery*	89.4	1	89.3	1	100	1	82.4	1
Chemoradiation	94.0	**1.84 (1.04 to 3.24)**	95.2	2.37 (0.77 to 7.24)	95.7	—	92.1	2.5 (0.66 to 9.36)
Treatment protocol								
Surgery only	89.5	1	89.1	1	100	1	100	1
Surgery plus radiation	89.3	0.97 (0.36 to 2.66)	90.3	1.15 (0.31 to 4.23)	100	—	78.6	—
Chemoradiation	94.0	1.83 (0.97 to 3.45)	95.2	2.43 (0.78 to 7.58)	95.7	—	92.1	—
Treatment adequacy								
Inadequate	90.4	1	95.2	1	94.2	1	85.3	1
Adequate	94.0	1.64 (0.94 to 2.85)	89.3	0.42 (0.14 to 1.30)	96.4	1.64 (0.41 to 6.60)	95.8	**4.00 (1.56 to 9.74)**
Time to FSA								
≤ 30 days	89.1	1	84.6	1	93.8	1	88.5	1
> 30 days	98.6	**8.53 (3.34 to 21.76)**	98.4	**11.45 (2.60 to 50.54)**	100	—	97.5	**5.00 (1.43 to 17.40)**

NOTE. Bold type indicates statistical significance.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; FSA, first specialist assessment; OR, odds ratio.

*Surgery only or combined with radiation and/or chemotherapy.

TABLE 4. Crude and Adjusted ORs for Delay on Treatment Initiation (> 60 days) in a Cohort of Women Diagnosed With Cervical Cancer, Rio de Janeiro, Brazil (2012 to 2014)

Characteristic	Crude OR (95% CI)	Adjusted OR (95% CI)*
Age, years	1.04 (1.02 to 1.07)	1.05 (1.02 to 1.08)
Stage		
IA-IIA	1	1
IIB-IIA	2.28 (1.05 to 4.91)	0.85 (0.30 to 2.40)
IIIB-IVA	1.03 (0.56 to 1.89)	0.38 (0.16 to 0.90)
Time to FSA		
≤ 30 days	1	1
> 30 days	8.53 (3.34 to 21.76)	11.52 (4.32 to 30.66)
Treatment protocol		
Surgery†	1	1
Chemoradiation	1.84 (1.04 to 3.24)	4.56 (1.81 to 11.47)
Treatment adequacy		
Inadequate	1	1
Adequate	1.64 (0.95 to 2.85)	2.57 (1.26 to 5.40)

Abbreviations: FSA, first specialist assessment; OR, odds ratio.
*Adjusted by education and all other variables in the model.
†Surgery only or surgery combined with radiation and/or chemotherapy.

developed countries have issued recommendations for good practice establishing that waiting times for radiotherapy initiation should not exceed 14 days, with a maximum acceptable delay of 28 days.[42-44] In our sample, the median time from diagnosis to treatment initiation presented no significant variation according to the type of first treatment (surgery or radiation), whereas the prevalence of treatment delay was greater than 80% in the surgery/radiation group. The multiple analyses showed that the chemoradiation protocol group had a chance of treatment delay 4.56 times higher than those treated with surgery/surgery plus radiation. Although such findings may still be affected by a residual confounding effect of the timing from diagnosis to FSA, the 60-day acceptable waiting time from diagnosis to treatment initiation was not achieved for the majority of our studied population. According to the regular cervical cancer care pathway (Fig 2), after the FSA, the time to treatment initiation depends on staging, treatment protocol definition, and preradiotherapy referral, which includes appraisal and prechemoradiation tests.

Treatment adequacy was highly associated with treatment delay, which is also related to stage and treatment protocol. Thus, women with adequate treatment were more likely to delay treatment initiation if they presented with late-stage disease (IIIB to IVA) at diagnosis (Table 3). Nevertheless, in the multivariable analysis, patients in the late stages were less likely to delay treatment. Such findings could be explained by the fact that women with late stages usually display symptoms such as pain, followed by bleeding, constipation, and so on.[33] Therefore, in a scenario of an opportunistic screening program, such patients are more likely to be diagnosed and seek a specialized center for treatment. Once they have their FSA, they are usually prioritized for treatment initiation, because several studies have shown that for every day of extension in overall treatment time, there is a loss of approximately 1% of local tumor control, particularly in patients with cervical cancer at stages III to IV.[45,46] However, because such patients often present with a poorer overall clinical condition, they are more likely to have unscheduled interruptions during radiotherapy, either prolonging the overall treatment time or interrupting the treatment because of toxicity, leading to a shorter interval from diagnosis to treatment completion.[15] Therefore, women with cervical cancer presenting at stages IIIB to IVA would frequently show more symptoms and poorer health conditions, leading doctors to prescribe a treatment protocol other than the one officially recommended for such stages to adjust to the patient's ability to bear the treatment's toxicity and adverse effects. However, the effect of adequate protocol combined with delay in treatment initiation on cervical cancer survival, according to stage at diagnosis, still must be investigated.

To our knowledge, this study was the first to evaluate delays in treatment initiation in a cohort of Brazilian women with cervical cancer, cross-tabling the HCR database with medical reports and histopathologic results. Also, this study has the largest sample size in the same cancer center in Brazil, allowing the evaluation of a group of patients receiving the same standard treatment protocol. This fact provides an opportunity to translate the findings directly into practice, because surveillance regarding the waiting time for treatment initiation could be implemented in a health care center. However, considering that this is a retrospective study, a few limitations must be addressed. First, we could not evaluate most patient factors that prevent health care–seeking and compliance. These factors include confusion or limited knowledge regarding the process of seeking and using preventive and specialized care services. They also include denial or fear, the precedence of competing obligations (transportation, financial, childcare, work labor, and so on) as a rationale for nonadherence to scheduled visits and test taking, embarrassment, and signs and symptoms before diagnosis. Second, although we were able to estimate the delays in cervical cancer treatment initiation at NCI in Brazil, the lack of information on medical reports about the reasons either the surgery was canceled or the radiation was scheduled for more than 2 weeks after treatment definition, as well as potential confounders such as screening history of cervical cancer, limited the analyses.

Increased treatment initiation delay (greater than 90%) was observed in a public specialized cancer center in Brazil, and the timing from diagnosis to the FSA was the main factor independently associated with such a delay. Age, chemoradiation, and adequate treatment were positively associated with treatment initiation delay, whereas stage at

diagnosis was inversely associated. Prospective studies identifying the competing factors related to patients and potential treatment initiation delays should be conducted in the future. Furthermore, the effect of treatment initiation delays on survival must also be investigated in the future.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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