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The impact of the distance traveled between residence and gestational trophoblastic neoplasia reference center and clinical outcomes in Brazilian women

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HIGHLIGHTS

- The distance between the patient's residence and GTN reference center (RC) is a risk factor for unfavorable outcomes.
- Living ≥56 km from the RC is associated with metastases, need for multiagent chemotherapy and loss to follow-up.
- Patients living long distances (≥56 km) for GTN-RC need special supportive care to facilitate optimal treatment and outcome.

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ABSTRACT

Objective. To relate the distance traveled from the patient's residence to the gestational trophoblastic neoplasia (GTN) reference center (RC) and the occurrence of unfavorable clinical outcomes, as well as to estimate the possible association between this distance and the risk of metastatic disease at presentation, the need for multiagent chemotherapy to achieve remission and loss to follow-up before remission.

Study design. Retrospective historical cohort study of patients with GTN followed at 8 Brazilian GTN-RC, from January 1st, 2000 - December 31st, 2017.

Results. Evaluating 1055 cases of GTN, and using a receiver operating characteristic curve, we found a distance of 56 km (km) from the residence to the GTN-RC (sensitivity = 0.57, specificity = 0.61) best predicted the occurrence of at least one of the following outcomes: occurrence of metastatic disease, need for multiagent chemotherapy to achieve remission, or loss to follow-up during chemotherapy. Multivariate logistic regression adjusted by age, ethnicity, marital status and the reference center location showed that when the distance between residence and GTN-RC was ≥56 km, there was an increase in the occurrence of metastatic disease (relative risk - RR:3.27; 95%CI:2.20–4.85), need for multiagent chemotherapy (RR:1.36; 95%CI:1.05–1.76), loss to follow-up

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during chemotherapy (RR:4.52; 95CI:1.93–10.63), occurrence of chemoresistance (RR:4.61; 95%CI:3.07–6.93), relapse (RR:10.27; 95%CI:3.08–34.28) and death due to GTN (RR:3.62; 95%CI:1.51–8.67).

Conclusions. The distance between the patient's residence and the GTN-RC is a risk factor for unfavorable outcomes, including death from this disease. It is crucial to guarantee these patients get prompt access to the GTN-RC and receive follow-up support.

1. Introduction

Gestational trophoblastic neoplasias (GTN) comprise a spectrum of malignant tumors that develop from an abnormal proliferation of trophoblastic tissue and may follow a hydatidiform mole or a nonmolar pregnancy [1,2]. The unique gestational nature of these tumors, with a high paternal genetic component and a very sensitive biomarker, human chorionic gonadotropin (hCG), allows high cure rates, even in chemoresistant and multimetastatic cases [3].

Although around 20,000 cases of GTN are diagnosed worldwide annually, this is one of the least common gynecological tumors [1,2]. Management is substantially better when performed in reference centers (RC) [4]. GTN treatment in a RC is the only modifiable variable associated with the lethality of the disease [5], which makes this specialized follow-up even more crucial. However, the need for regular follow-up in GTN-RC brings numerous difficulties, including traveling considerable distances to receive proper treatment, which has been reported as an adverse prognostic factor in other diseases [6–11].

Few studies have investigated the impact of distance traveled between the patient's residence and the RC on GTN prognosis, and the results have been mixed [12,13]. None of these studies determined a discriminatory distance to be traveled by the patient to the health care service after which unfavorable outcomes would be observed, instead extrapolating distance references associated with adverse outcomes from tumors other than GTN [6–11].

While Brazil has established a GTN-RC network [14,15], its continental dimension makes it even more challenging not only to guarantee the treatment of GTN patients in these specialized centers, but also to avoid delays in referrals and abandonment of treatment due to difficulties in reaching a RC. However, no study has evaluated in depth the impact of the distance traveled by patients with GTN to the RC and the prognosis of this disease, using cutoff points for distance specifically obtained from GTN patients.

The aim of this study is to find the distance traveled from the residence of the patient to the GTN-RC after which the occurrence of unfavorable clinical outcomes increases, as well as to estimate the possible association between this distance and the risk of metastatic disease at the presentation, the need for multiagent chemotherapy to achieve remission and loss to follow-up before remission. This study is especially important for health managers to establish care policies aimed at shortening the time between the GTN diagnosis and the referral to the GTN-RC for immediate treatment, as well as for healthcare providers specializing in GTN, to increase attention to patients whose distance between home and the RC may be an adverse prognostic risk factor.

2. Material and methods

2.1. Study design

This is a longitudinal, retrospective, collaborative multicenter, nonconcurrent cohort study of patients with GTN followed at 8 different Brazilian GTN RC, from January 1st, 2000, to December 31st, 2017. All GTN RC in Brazil have the same minimal functioning criteria, among which included the presence of 1 medical oncologist, 1 obstetrician gynecologist, 1 pathologist, 1 nurse and 1 social worker, all with special interest in GTD. All data were obtained through direct evaluation of medical records. This study was approved by the local Institutional Review Board from each RC, as presented in the Supplemental Table 1. The study was done with anonymized patient records, so the Ethics Committees waived the need for obtaining individual informed consent.

For the design of this study, we have followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [16].

2.2. Study participants

The participants in this study were women treated for GTN according to the International Federation of Gynecology and Obstetrics (FIGO) criteria [17]. Furthermore, all centers in this study used, during the analyzed period, the same criteria for diagnosis and treatment, such as criteria for chemoresistance, as established by the Brazilian GTN consensus, aligned with FIGO. All patients were followed for at least 2 years after remission to detect relapse. Therefore, the last patients included in December 2017 were followed at least until December 2019. Due to the Covid-19 pandemic, and extra difficulties in referring GTN patients, we decided not to include patients seen from 2020 onwards in this study [18].

Likewise, cases of patients who changed address during treatment, became pregnant <12 months after remission, that came from other countries or had at least part of the follow-up made by telemedicine, those with histopathological diagnosis of placental site trophoblastic tumor and epithelioid trophoblastic tumor, as well as the cases with missing data were also excluded.

2.3. Diagnosis and treatment of postmolar gestational trophoblastic neoplasia

Management of patients in terms of GTN diagnosis and treatment followed FIGO protocols, as presented in Supplemental Table 2 [17].

2.4. Outcomes and variables

The primary outcomes were the occurrence of metastatic disease (assessed by FIGO criteria [17]), the need for multiagent chemotherapy to achieve remission and loss to follow-up before remission (while undergoing chemotherapy). The secondary outcomes were the occurrence of chemoresistance (defined as hCG levels in plateau or increase over two cycles of chemotherapy), GTN relapse (defined as the occurrence of re-elevation of hCG levels after 4 weeks from remission) and death due to GTN.

The following demographic variables were evaluated: age (in years), number of gestations and pregnancies, ethnicity (white, black, brown, yellow, other, obtained through self-declaration as defined by the Brazilian Institute of Geography and Statistics) and marital status (with or without partner). The distance between the patient's residence and the GTN-RC (in kilometers) was obtained using the Google Maps® software [19].

Treatment variables included the time between the end of pregnancy and the beginning of chemotherapy (in months), pretreatment hCG level (international unit per liter [IU/L]), initiation of chemotherapy outside the RC, choice of chemotherapy not complying with the FIGO

criteria, type of chemotherapy (single vs. multiagent regimen), time to remission (defined as the time from the initiation of chemotherapy to the third hCG level < 5 IU/L, in months) and number of chemotherapy consolidation cycles (defined as chemotherapy given after GTN remission).

2.5. Statistical analysis

Descriptive analysis was used to characterize the study population. Categorical variables were described in the text and tables as absolute (N) and relative frequencies (%), while continuous variables appear as medians and interquartile ranges (IQR).

Chi-square test and Mann-Whitney *U* test were used to compare proportions and continuous variables respectively.

The forest plot represents the logistic regression used to estimate crude (cOR) and age-adjusted odds ratios (aOR) with 95% confidence intervals (95% CI). Patient age, ethnicity, marital status and RC location were assessed as possible confounding variables in the model between predictors and outcome. Age is an established risk factor for GTN aggressiveness [5]. Likewise, black women in Brazil and those without partners are more likely present with a more advanced cancer diagnosis due to difficulties with access to care [20,21]. These access difficulties may also vary according to the local organization of the health care network where the RC is located in Brazil [22]. Combined variables evaluates cases in which there was at least one of the primary outcomes, as well as at least one of the secondary outcomes. A Poisson regression model was performed to test the regression coefficients. To select a cut-off distance for discriminating adverse primary outcomes, we created a receiver operating characteristic curve (ROC) examining adverse outcomes as a function of distance and selected the point based on Youden's index which maximized sensitivity and specificity [23].

Statistical analyses and the forest plot were performed using SAS, version 9.4.

Because the sample size included all eligible study subjects within the study period, we performed a post-hoc power calculation, using the online PSS Health tool. The power to test whether there is a difference between the percentages of metastatic disease at presentation, need for multiagent chemotherapy to achieve remission and lost to follow-up [14], considering the cutoff of 56 km for the distance from the residence of the patient to the GTN-RC, is 99, 80.9 and 94.1%, respectively, considering an alpha level of 0.05.

3. Results

Fig. 1 is a flow diagram summarizing the derivation of the study population. Among 1851 patients treated between 2000 and 2017 at the participating RC, 1055 cases of GTN were included.

Table 1 shows demographic and clinical presentation as well as therapeutic outcomes among GTN patients evaluated in 8 different RC throughout Brazil. This population is formed by mainly young women (median of 28 years old), mostly self-declared white (54.3%) and partnered (72.6%). They took 2 months to initiate chemotherapy after the end of pregnancy, with a median pretreatment hCG of 17,730 IU/L. There were few GTN cases that initiated chemotherapy outside the RC (7.5%) or received chemotherapy in disagreement with the FIGO criteria (3.5%). Although most cases were non-metastatic (86.6%) low-risk GTN (81.3%), multiagent chemotherapy was needed in 26.4% of patients to achieve remission. A median of 2.5 months was needed to attain remission, with only 2.9% loss to follow-up during treatment and 8.5% dropout from follow-up <12 months from remission. Only 40% of the patients received at least 3 cycles of consolidation chemotherapy, developing chemoresistance in 13.9%, relapse in 2.6% and death due to GTN in 2.7%. The differences in the distances traveled from the residence to the 8 Brazilian GTN-RC included in this study were significant (median of 50 km - km, *p*-value <0.01), reflecting the different geographic scenarios where these specialized services operate.

Based on the ROC curve, an optimal cutoff distance of 56 km (sensitivity = 0.57, specificity = 0.61) predicted the occurrence of at least one of the three primary study outcomes: occurrence of metastatic disease, need for multiagent chemotherapy to achieve remission, or abandonment of follow-up during chemotherapy (Fig. 2).

Table 2 shows that the distance between the patient's residence and the GTN-RC was significantly associated with more unfavorable outcomes, regardless of whether 80 km, often cited in access studies, or 56 km, determined empirically from the present study, was considered. When we analyzed the effect of distance using the cutoff for GTN

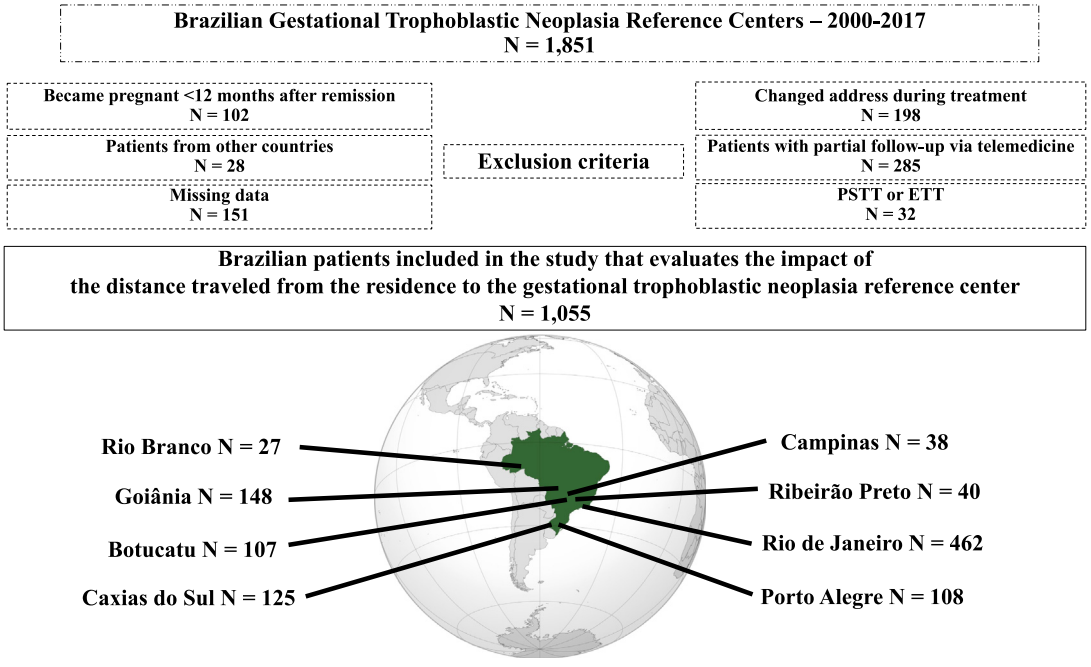

Fig. 1. Flow diagram summarizing the derivation of the study population.

Table 1
Demographic and clinical presentation and therapeutic outcomes among patients with gestational trophoblastic neoplasia (GTN) followed at 8 Brazilian Reference Centers (RC), between the years 2000–2017.

Variables	Brazil (N = 1055)	Rio de Janeiro (N = 462)	Campinas (N = 38)	Ribeirão Preto (N = 40)	Botucatu (N = 107)	Goiânia (N = 148)	Porto Alegre (N = 108)	Caxias do Sul (N = 125)	Rio Branco (N = 27)	p-value
Age in years[1]	28 (22–34)	31 (24–35)	30 (18–37)	28 (22−31)	26 (21−32)	25 (20–31.5)	28 (24–36)	27 (22−33)	25 (19–35)	<0.01
Number of gestation[1]	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–4)	2 (1–3)	2 (1–2)	2 (1–3)	2 (1–3)	2 (2–4)	<0.01
Parity[1]	1 (0–1)	1 (0–1)	0.5 (0–1)	1 (0–2)	1 (0–2)	0 (0–1)	1 (0–2)	1 (0–1)	1 (0–3)	0.01
Ethnicity (self declared) (N/%)										< 0.01
white	572 (54.3)	165 (35.7)	24 (63.1)	32 (80)	83 (77.6)	101 (68.2)	57 (53.8)	107 (85.6)	3 (11.1)	
non-white	481 (45.7)	297 (64.3)	14 (36.9)	8 (20)	24 (22.4)	47 (31.8)	49 (46.2)	18 (14.4)	24 (88.9)	
Marital status (self declared) (N/%)										< 0.01
with partnership	751 (72.6)	295 (63.8)	12 (66.77)	23 (57.5)	84 (78.5)	136 (91.9)	63 (58.9)	121 (96.8)	17 (63)	
without partnership	283 (27.4)	167 (36.2)	6 (33.3)	17 (42.5)	23 (21.5)	12 (8.1)	44 (41.1)	4 (3.2)	10 (37)	
Distance between residence and RC (in kilometers)	50 (25–84)	50 (29–76)	35.7 (27–74)	63.5 (39–90)	102 (71–190)	27 (13–171)	45 (15–78)	91 (20−112)	90 (6.9–229)	<0.01
Time[2] to initiate chemotherapy (CHX) in months[1]	2 (1–4)	2 (1–4)	5.5 (4–10)	2 (1–3)	2 (1.4–3.4)	2 (2–3)	2 (1–3)	2 (1–3)	3 (2–4)	<0.01
Pretreatment human chorionic gonadotropin level (IU/L) (median and interquartile range)	17,730 (4232-63,177)	20,000 (5000-86,000)	67,343 (8000-238,729)	15,466.5 (6360.0-55,426.0)	13,441 (4200-52,582)	24,602.0 (9923.5-36,557.0)	4227 (1130-28,740)	12,862 (2460-82,346)	5730 (1000-28,437)	<0.01
CHX initiated outside the RC	79 (7.5)	61 (13.2)	0 (0)	0 (0)	5 (4.6)	2 (1.3)	9 (8.3)	0 (0)	2 (7.4)	< 0.01
CHX initiated in disagreement with FIGO[3] criteria	38 (3.5)	34 (7,2)	0 (0)	1 (2.5)	0 (0)	2 (1.4)	1 (1)	0 (0)	0 (0)	< 0.01
FIGO[3] stage										< 0.01
I	913 (86.6)	395 (85.5)	29 (76.3)	31 (77.5)	82 (76.6)	140 (94.6)	104 (97.2)	109 (87.2)	23 (85.2)	
II	26 (2.5)	10 (2.2)	0 (0)	1 (2.5)	5 (4.7)	2 (1.3)	2 (1.9)	6 (4.8)	0 (0)	
III	89 (8.4)	43 (9.3)	7 (18.4)	4 (10)	19 (17.7)	6 (4.1)	1 (0.9)	6 (4.8)	3 (11.1)	
IV	26 (2.5)	14 (3)	2 (5.3)	4 (10)	1 (1)	0 (0)	0 (0)	4 (3.2)	1 (3.7)	< 0.01
FIGO[3] score	3 (2–5)	4 (3–7)	4 (2–6)	2 (2–4)	3 (1–5)	3 (3–3)	4 (1–7)	2 (1–3)	1 (0–3)	< 0.01
≤6	857 (81.3)	338 (73.2)	33 (86.8)	32 (80)	89 (83.2)	146 (98.6)	73 (68.2)	122 (97.6)	24 (88.9)	
7–12	177 (16.8)	118 (25.5)	3 (7.9)	6 (15)	12 (11.2)	1 (0.7)	32 (29.9)	3 (2.4)	2 (7.4)	
≥ 13	20 (1.9)	6 (1.3)	2 (5.3)	2 (5)	6 (5.6)	1 (0.7)	2 (1.9)	0 (0.00)	1 (3.7)	
Metastatic disease at presentation	141 (13.4)	67 (14.5)	9 (23.7)	9 (22.5)	25 (23.4)	8 (5.4)	3 (2.8)	16 (12.8)	4 (14.8)	< 0.01
CHX regimen needed to remission										< 0.01
single agent	776 (73.6)	335 (72.5)	26 (68.4)	31 (77.5)	84 (78.5)	141 (95.3)	54 (50)	80 (64)	25 (92.6)	
multiagente regimen	279 (26.4)	127 (27.5)	12 (31.6)	9 (22.5)	23 (21.5)	7 (4.7)	54 (50)	45 (36)	2 (7.4)	
Time to remission in months[1]	2.5 (2–4)	2 (1–3)	4 (3–5)	3 (2–4)	2.5 (1.8–4.0)	3 (2–4)	3 (1–3)	3 (2–5)	3 (2–3)	<0.01
Lost to follow-up during CHX	31 (2.9)	20 (4.3)	0 (0)	2 (5)	1 (0.9)	1 (0.7)	5 (4.6)	0 (0)	2 (7.4)	0.03
Lost to follow-up <12 months from remission	89 (8.5)	40 (8.7)	0 (0)	6 (15)	1 (0.9)	30 (20.8)	3 (2.8)	0 (0)	9 (33.3)	< 0.01
Consolidation chemotherapy										<0.01
≥ 3 cycles	420 (40)	317 (68.6)	2 (5.3)	3 (7.5)	1 (1)	6 (4.2)	87 (80.6)	2 (1.6)	2 (7.4)	
≤ 2 cycles	631 (60)	145 (31.4)	36 (94.7)	37 (92.5)	106 (99)	138 (95.8)	21 (19.4)	123 (98.4)	25 (92.6)	
Chemoresistance	146 (13.9)	94 (20.3)	9 (23.7)	4 (10)	24 (22.4)	9 (6.2)	2 (1.8)	4 (3.2)	0 (0)	< 0.01
Relapse	27 (2.6)	19 (4.1)	0 (0)	1 (2.6)	6 (5.7)	1 (0.7)	0 (0)	0 (0)	0 (0)	0.01
Death due to GTN	29 (2.7)	13 (2.8)	3 (7.9)	1 (2.6)	3 (2.8)	4 (2.70	1 (0.9)	3 (2.4)	1 (3.7)	0.68

[1] Median and interquartile range.
[2] Time between the end of pregnancy and the beginning of chemotherapy
[3] FIGO – International Federation of Obstetrics and Gynecology.

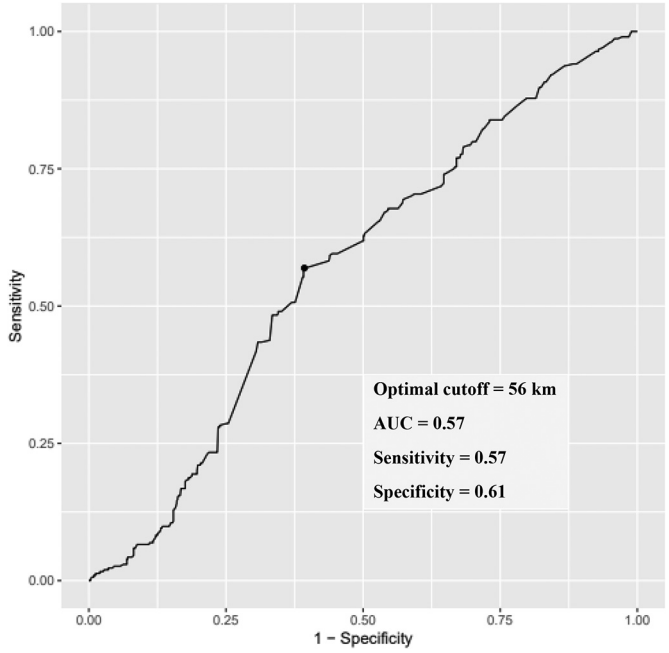

Fig. 2. Receiver operating characteristic curve demonstrating the optimal cutoff of distance from the residence to the gestational trophoblastic neoplasia reference center for the occurrence of, at least, one of the three primary study outcomes: occurrence of metastatic disease at presentation, need for multiagent chemotherapy to achieve remission, or abandonment of follow-up during chemotherapy among Brazilian patients.

Brazilian patients, we observed that when the distance between the patient's residence and the RC was ≥56 km, there was a significant delay in starting chemotherapy (3 versus 2 months, $p < 0.01$), greater initiation of treatment outside the RC (10.77 versus 6.10%, $p < 0.01$), treatment in disagreement with FIGO criteria (6.8 versus 1.5%), occurrence of metastatic disease at presentation (21.7 versus 7%, $p < 0.01$), FIGO score 7–12 (23.4 versus 14.7%, $p < 0.01$) and ≥ 13 (4.4 versus 0.2%, $p < 0.01$), higher occurrence of follow-up abandonment, both during chemotherapy (5.4 versus 1.3%, $p < 0.01$) and < 12 months after remission (14.1 versus 5.5%, $p < 0.01$), as well as a higher occurrence of chemoresistance (26.1% versus 5.9%, $p < 0.01$), higher number of patients that received an incomplete number (≤ 2 cycles) of consolidation chemotherapy cycles (65 versus 48.3%, $p < 0.01$), greater occurrence of relapse (5.67 versus 0.57%, $p < 0.01$) and death due to GTN (4.92 versus 1.33%, $p < 0.01$), in relation to those who lived <56 km from the GTN-RC, respectively.

Both the univariate logistic regression and the multivariate logistic regression adjusted by age, ethnicity, marital status and the reference center location showed that the distance between the residence and the GTN-RC were associated with an increase in the RR of unfavorable GTN outcomes, most of the time regardless of whether the cutoff of 80 or 56 km was used, as shown in Table 3 and Fig. 3. Time to initiate chemotherapy ≥7 months, pretreatment hCG ≥ 100,000 IU/L, chemotherapy initiated outside the RC, chemotherapy initiated in disagreement with FIGO criteria, FIGO score ≥ 7 and time to remission ≥4 months were associated with unfavorable outcomes in the multivariate logistic regression. In the same way, when the distance between residence and GTN-RC was ≥56 km, there was an increase in the occurrence of metastatic disease

Table 2
Correlation between the distance from the residence of Brazilian patients with gestational trophoblastic neoplasia (GTN) to the Reference Center and demographic, clinical characteristics and therapeutic outcomes.

Variables	Distance from the residence of GTN patient to the reference center					
	< 80 km (*N* = 628)	≥ 80 km (*N* = 325)	p-value	< 56 km (*N* = 525)	≥ 56 km(*N* = 428)	p-value
Age in years[1]	29 (23–34)	27 (21–34)	0.03	29 (23–35)	28 (22–34)	0.03
Number of gestation[1]	2 (1–3)	2 (1–3)	0.82	2 (1–2)	2 (1–3)	0.13
Parity[1]	1 (0–1)	1 (0–2)	0.65	1 (0–1)	1 (0–2)	0.40
Ethnicity (self declared) (N/%)			0.03			0.27
white	303 (48.3)	181 (55.7)		258 (49.2)	226 (52.8)	
non-white	324 (51.7)	144 (44.3)		266 (50.8)	202 (47.2)	
Marital status (self declared) (N/%)			0.39			0.11
with partnership	422 (68.9)	230 (71.6)		346 (67.7)	306 (72.5)	
without partnership	190 (31.1)	91 (28.4)		165 (32.3)	116 (27.6)	
Time[2] to initiate chemotherapy (CHX) in months[1]	2 (1–3)	3 (2–5)	<0.01	2 (1–3)	3 (2–5)	<0.01
Pretreatment human chorionic gonadotropin level (IU/L)[1]	15,000 (4000-48,354.5)	27,451 (5912-116,432)	<0.01	14,033 (4000-42,876)	27,937.5 (5667.5-115,215)	<0.01
CHX initiated outside the RC (N/%)	38 (6.1)	40 (12.3)	<0.01	32 (6.10)	46 (10.77)	<0.01
CHX initiated in disagreement with FIGO[3] criteria (N/%)	13 (1.9)	25 (7.7)	<0.01	8 (1.5)	30 (6.8)	<0.01
FIGO[3] stage (N/%)			<0.01			<0.01
I	575 (91.6)	248 (76.3)		488 (92.9)	335 (78.3)	
II	10 (1.6)	11 (3.4)		7 (1.3)	14 (3.3)	
III	36 (5.7)	49 (15.1)		24 (4.6)	61 (14.2)	
IV	7 (1.1)	17 (5.2)		6 (1.1)	18 (4.2)	
FIGO[3] score (N/%)	3 (2–5)	3 (2–7)	<0.01	3 (2–4)	3 (2–7)	<0.01
≤6	513 (81.7)	243 (74.8)		447 (85.1)	309 (72.2)	
7–12	113 (18)	64 (19.7)		77 (14.7)	100 (23.4)	
≥ 13	2 (0.3)	18 (5.5)		1 (0.2)	19 (4.4)	
Metastatic disease at presentation (N/%)	53 (8.4)	77 (23.7)	<0.01	37 (7)	93 (21.7)	<0.01
CHX regimen needed to remission (N/%)			0.37			<0.01
single agent	471 (75)	235 (72.3)		408 (77.7)	298 (69.6)	
multiagente regimen	157 (25)	90 (27.7)		117 (22.3)	130 (30.4)	
Time to remission in months[1]	2 (1–3)	3 (2–4)	<0.01	2 (1–3)	3 (2–4)	<0.01
Lost to follow-up during CHX (N/%)	11 (1.7)	19 (5.9)	<0.01	7 (1.3)	23 (5.4)	<0.01
Lost to follow-up <12 months from remission (N/%)	38 (6.1)	51 (15.8)	<0.01	29 (5.5)	60 (14.1)	<0.01
Chemoresistance (N/%)	60 (9.6)	82 (25.4)	<0.01	31 (5.9)	111 (26.1)	<0.01
Consolidation chemotherapy			<0.01			<0.01
≥ 3 cycles	333 (53.1)	87 (27)		271 (51.7)	149 (35)	
≤ 2 cycles	294 (46.9)	235 (73)		253 (48.3)	276 (65)	
Relapse (N/%)	9 (1.44)	18 (5.63)	<0.01	3 (0.57)	24 (5.67)	<0.01
Death due to GTN (N/%)	9 (1.43)	19 (5.86)	<0.01	7 (1.33)	21 (4.92)	<0.01

[1] Median and interquartile range.
[2] Time between the end of pregnancy and the beginning of chemotherapy.
[3] FIGO – International Federation of Obstetrics and Gynecology.

Table 3
Univariate logistic regression analyzing demographic, clinical and therapeutic variables associated with the occurrence of primary and secondary outcomes related to the prognosis of Brazilian patients with gestational trophoblastic neoplasia treated between 2000 and 2017.

Variables	Crude RR (CI 95%)							
	Primary outcomes							
	Metastatic disease	p-value	Multiagent chemotherapy to remission	p-value	Lost to follow-up during chemotherapy	p-value	Combined variables	p-value
Age ≥ 40 years	1.25 (0.79–1.99)	0.34	1.03 (0.72–1.47)	0.86	1.10 (0.38–3.15)	0.86	0.98 (0.71–1.36)	0.92
Non-white ethnicity	1.11 (0.80–1.54)	0.54	1.07 (0.84–1.35)	0.59	4.74 (1.94–11.60)	<0.01	1.10 (0.89–1.36)	0.37
Marital status without partnership	1.43 (1.01–2.03)	0.04	1.53 (1.20–1.96)	<0.01	2.65 (1.30–5.43)	<0.01	1.42 (1.14–1.78)	<0.01
Distance ≥80 km	2.81 (1.98–3.98)	<0.01	1.11 (0.85–1.43)	0.44	3.36 (1.60–7.07)	<0.01	1.39 (1.10–1.74)	<0.01
Distance ≥56 km	3.08 (2.11–4.51)	<0.01	1.36 (1.06–1.75)	0.01	4.05 (1.73–9.44)	<0.01	1.62 (1.29–2.03)	<0.01
Time[1] to initiate chemotherapy ≥7 months	5.21 (3.61–7.54)	<0.01	2.12 (1.51–2.99)	<0.01	0.94 (0.22–3.93)	0.93	2.31 (1.71–3.12)	<0.01
Pretreatment human chorionic gonadotropin ≥100,000 IU/L	7.98 (5.63–11.30)	<0.01	3.25 (2.57–4.12)	<0.01	1.71 (0.79–3.71)	0.18	2.94 (2.37–3.65)	<0.01
Chemotherapy initiated outside the Reference Center	3.67 (2.47–5.44)	<0.01	2.07 (1.48–2.89)	<0.01	3.74 (1.61–8.72)	<0.01	2.43 (1.83–3.24)	<0.01
Chemotherapy initiated in disagreement with FIGO[2] criteria	5.26 (3.45–8.33)	<0.01	1.56 (0.93–2.63)	0.09	5.56 (2.08–14.29)	<0.01	2.44 (1.67–3.57)	<0.01
FIGO[2] score								
≤ 7	1.00		1.00		1.00		1.00	
7–12	8.69 (6.01–12.57)	<0.01	8.05 (6.27–10.35)	<0.01	1.61 (0.68–3.78)	0.28	5.77 (4.63–7.19)	<0.01
≥ 13	17.53 (10.13–30.33)	<0.01	7.43 (4.44–12.44)	<0.01	4.28 (1.00–18.26)	0.05	5.87 (3.68–9.37)	<0.01
Time to remission ≥4 months	1.84 (1.31–2.58)	<0.01	1.39 (1.08–1.78)	<0.01	1.54 (0.73–3.23)	0.26	2.24 (1.76–2.85)	<0.01

Variables	Secondary outcomes							
	Chemoresistance	p-value	Relapse	p-value	Death due to GTN	p-value	Combined variables	p-value
Age ≥ 40 years	0.95 (0.57–1.57)	0.84	2.04 (0.82–5.04)	0.12	1.49 (0.57–3.91)	0.41	1.08 (0.68–1.71)	0.73
Non-white ethnicity	1.24 (0.89–1.71)	0.20	2.02 (0.93–4.42)	0.08	1.28 (0.62–2.65)	0.51	1.16 (0.85–1.58)	0.35
Marital status without partnership	1.12 (0.78–1.61)	0.54	0.76 (0.31–1.89)	0.56	1.57 (0.72–3.42)	0.26	1.09 (0.77–1.54)	0.64
Distance ≥80 km	2.65 (1.90–3.70)	<0.01	3.92 (1.76–8.72)	<0.01	4.09 (1.85–9.04)	<0.01	2.74 (1.99–3.76)	<0.01
Distance ≥56 km	4.40 (2.96–6.56)	<0.01	9.91 (2.98–32.91)	< 0.01	3.69 (1.57–8.68)	<0.01	4.28 (2.94–6.23)	<0.01
Time[1] to initiate chemotherapy ≥7 months	4.29 (2.93–6.27)	<0.01	3.88 (1.56–9.61)	<0.01	12.54 (6.05–25.98)	<0.01	4.16 (2.89–5.98)	<0.01
Pretreatment human chorionic gonadotropin ≥100,000 IU/L	5.66 (4.08–7.86)	<0.01	3.92 (1.84–8.33)	<0.01	15.87 (6.46–38.99)	<0.01	5.36 (3.92–7.32)	<0.01
Chemotherapy initiated outside the Reference Center	4.85 (3.38–6.96)	<0.01	6.13 (2.76–13.65)	<0.01	11.51 (5.55–23.84)	<0.01	4.68 (3.31–6.62)	<0.01
Chemotherapy initiated in disagreement with FIGO[2] criteria	5.26 (3.45–8.33)	<0.01	1.56 (0.93–2.63)	0.09	5.56 (2.08–14.29)	<0.01	2.44 (1.67–3.57)	<0.01
FIGO[2] score								
≤ 7	1.00		1.00		1.00		1.00	
7–12	8.69 (6.01–12.57)	<0.01	8.05 (6.27–10.35)	<0.01	1.61 (0.68–3.78)	0.28	5.77 (4.63–7.19)	<0.01
≥ 13	17.53 (10.13–30.33)	<0.01	7.43 (4.44–12.44)	<0.01	4.28 (1.00–18.26)	0.05	5.87 (3.68–9.37)	<0.01
Time to remission ≥4 months	1.84 (1.31–2.58)	<0.01	1.39 (1.08–1.78)	<0.01	1.54 (0.73–3.23)	0.26	2.24 (1.76–2.85)	<0.01

[1] Time between the end of pregnancy and the beginning of chemotherapy.
[2] FIGO – International Federation of Obstetrics and Gynecology.

at presentation (RR: 3.27, 95% CI: 2.20–4.85), need for multiagent chemotherapy to achieve remission (RR: 1.36, 95% CI: 1.05–1.76), loss to follow-up during chemotherapy (RR: 4.52, 95% CI: 1.93–10.63) or the combination of at least one of these outcomes (RR: 1.62, 95% CI: 1.29–2.05), as well as the occurrence of chemoresistance (RR: 4.61, 95% CI: 3.07–6.93), relapse (RR: 10.27, 95% CI: 3.08–34.28), death due to GTN (RR: 3.62, 95% CI: 1.51–8.67) or the combination of at least one of these outcomes (RR: 4.39, 95% CI: 2.99–6.45), as shown in Fig. 3.

4. Discussion

In this study, after multivariate logistic regression, adjusted for age, ethnicity, marital status and reference center location, we identified that when the distance between the residence of GTN Brazilian patients and the RC was ≥56 km, there was an increase in the occurrence of the following adverse outcomes: metastatic disease at presentation, need for multiagent chemotherapy to achieve remission and withdrawal from follow-up during chemotherapy, as well as chemoresistance, relapse of GTN and death due to GTN.

Most guidelines recommend that GTN be treated in a RC [1,22,24–26]. However, few studies have evaluated the impact of this recommendation, in terms of the distance traveled between the patient's residence and the GTN-RC, the possible access difficulties due to this distance, and the prognosis of disease [12,13,27,28]. Our results are similar to the work of Feltmate, et al, who reported that for patients undergoing post-molar hCG surveillance in New England, that if a distance from the patient's residence to the RC was farther than 32 km there was significantly higher likelihood of these patients not completing hCG follow-up [27]. Maesta, et al, likewise examined Brazilian patients with molar pregnancies followed after uterine evacuation outside the RC due to the long distance between the patient's residence and the RC. Patients followed outside the RC who were ultimately referred to these specialized services later presented with 8 times more metastatic disease (48.1 versus 5.9%) compared to those who were followed immediately after uterine evacuation in a RC [28].

We identified only 2 others studies that specifically assessed the impact of distance between the GTN patient's home and the RC, which showed divergent results [12,13]. Makhathinia, et al, evaluated 33 patients with GTN from Pietermaritzburg (South Africa) and did not find a statistically significant association between the distance traveled by patients and the FIGO stage and score, the time to initiate chemotherapy or deaths due to GTN, showing that distance ≥80 km between the

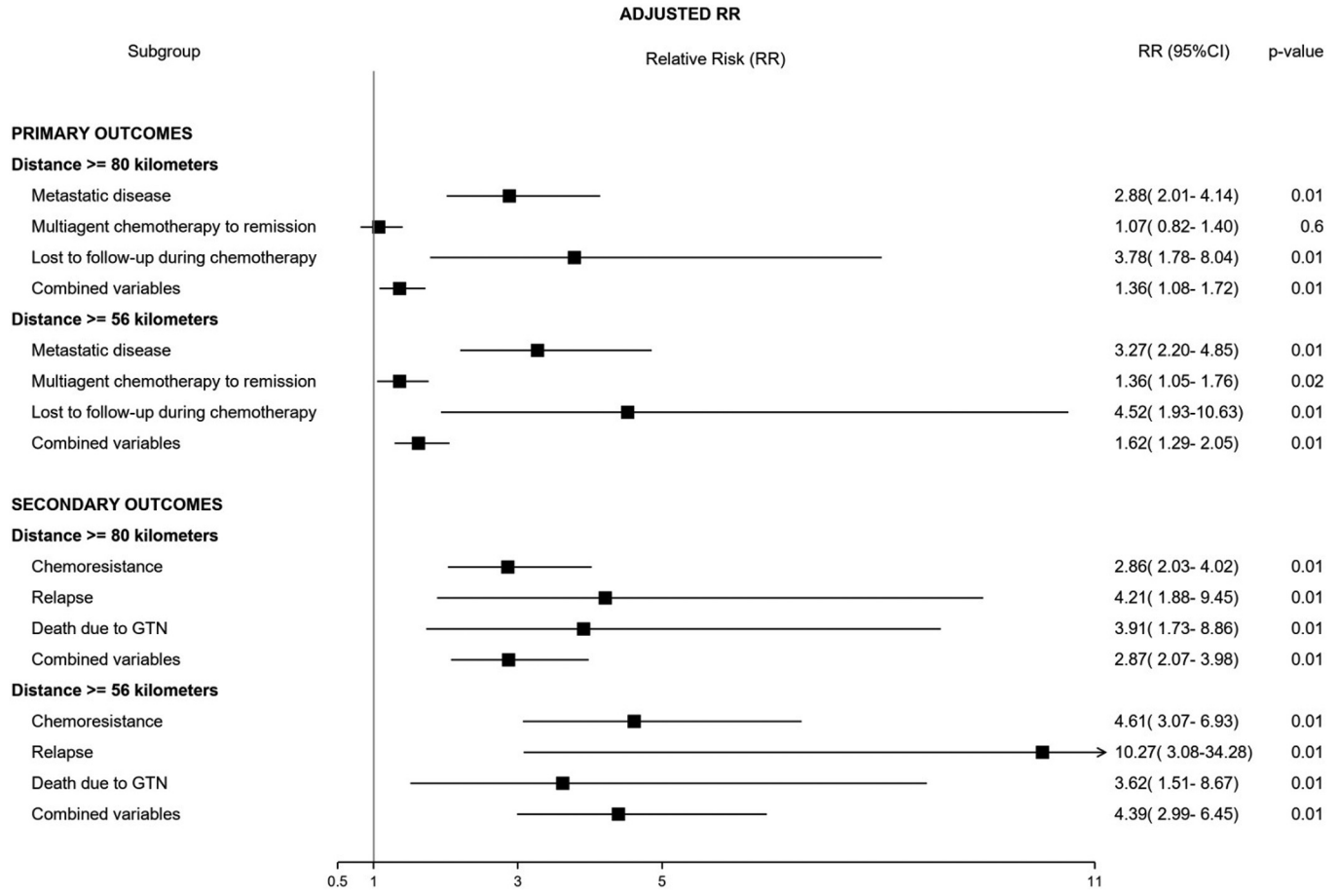

Fig. 3. Forest plot showing multivariate Poisson regression, adjusted by maternal age, ethnicity, marital status and the reference center location evaluating the relative risk (RR) for the occurrence of the primary and secondary outcomes studied among patients with gestational trophoblastic neoplasia followed at 8 Brazilian different reference centers, between the years 2000–2017. CI - confidence interval. *p*-value evaluated by Poisson regression. Combined variables refer to any of the total composite results of those listed among the primary and secondary outcome variables.

patient's residence and the RC was only associated with loss of follow-up (27%) [13]. However, the authors did not evaluate whether this abandonment of follow-up occurred during treatment or < 12 months after remission. The other study by Clark, et al, evaluated 60 patients with GTN from Chapel Hill (United States) and found an association between high-risk GTN and need for multiagent chemotherapy and distances between the patient's residence and the GTN-RC ≥ 80 km [12]. Both studies involved few patients and used the 80 km cutoff to estimate the potential effect of distance from the patient's residence and the GTN-RC based on studies in the literature, related to other tumors [6–11], which may have influenced the results.

The Brazilian public health system has organized care for patients with GTN in a RC [29]. Once diagnosed with GTN, patients are referred from the public regulation system to GTN RC, as agreed by the line of care for women with GTD, established by the Brazilian Ministry of Health [29]. Additionally, patients can obtain care at RC directly, without the need for official referral, which also applies to those coming from the private or supplementary health system, since the RC work with an open door to care for everyone with GTD [15]. This referral model, in a country of continental dimensions, is ideal for estimating the potential effect of the distance from the patient's home to the RC and the prognosis of GTN. We found an increased RR for the occurrence of multiple unfavorable outcomes when the distance between the patient's residence and the GTN-RC was ≥56 km, signaling a clear impact of how distance adversely influences care at specialized services. This was associated not only with greater clinical aggressiveness (such as the occurrence of metastatic disease at presentation) but also demanded more intensive and expensive multiagent treatments to achieve remission. More extensive disease and the need for more intensive treatment to achieve remission aggravates the problem of follow-up in cases with long distances between home and the GTN-RC.

Distance was also associated with a higher risk of patients dropping out of treatment and follow-up while undergoing chemotherapy, as well as being associated with incomplete consolidation chemotherapy protocols. Studies have shown a higher occurrence of GTN relapse when patients received ≤2 cycles of consolidation chemotherapy compared to patients who received ≥3 cycles [30,31]. This may have contributed to a higher occurrence of relapse among our patients. Furthermore, the feeling of security after hCG normalization, associated with the long distances between home and the GTN-RC, may have motivated the reduction in the number of cycles of consolidation chemotherapy in these patients.

Ultimately, Brazilian patients with GTN who live farther from the RC are at greater risk of dying from this disease and should receive psychosocial support to lessen the impact of this variable on their prognosis. In a recent study on the lethality of Brazilian patients with GTN, we identified that the occurrence of metastatic disease (RR: 18.88) and the initial treatment outside the Reference Center (RR: 2.91) were associated with the occurrence of death due to GTN [5]. The current study adds to the prior work by showing that the distance between the residence of Brazilian patients with GTN and the RC ≥ 56 km is also associated with death due to GTN.

It is not entirely clear why, when compared to women living >56 km from RC to those living >80 km from the RC, there would be statistically more women requiring multiagent chemotherapy to achieve remission for those at >56 km but no difference for those that lived >80 km. It is unlikely that there is something biologically different between these cases of GTN and therefore it likely has to do with other socioeconomic and environmental factors. This result may reflect free medical tranportation, which is guarenteed for those living in other cities, which is more common where the distance from the residence to the RC of >80 km is a factor. The adverse effects of living at greater distance from the RC may be partly mitigated in patients by the availability of free transport when the distance from home to RC exceeded 80 km.

Our study does have several limitations. The retrospective nature of the analysis of data from medical records needs to be highlighted as a bias in the study design. Although the GTN RC is a variable that can be associated with several biases in this study, not only considering the number of patients treated by each RC and the expertise generated by this, but also due to regional differences linked to the location of these RCs (such as access difficulties, road infrastructure, transport network, etc.). We therefore included the RC among the adjustment variables in the multivariate logistic regression analysis, and we nullified, as much as possible, the potential effect of this confounder in our study. Furthermore, as far as we know, this is the first study to obtain from a robust sample of 1055 GTN cases evidence that the distance between the patient's home and the RC significantly contributes to multiple adverse clinical outcomes.

Given the low occurrence of GTN and the complexity of a RC, it is essential that these specialized services provide support for primary care health professionals as well as guidance for patients. This is especially important for serving regions with low population density, limited resources, or remote areas [32]. In this sense, three successful experiences can be applied where there are long distances between the patient's residence and the GTN-RC. The first is related to clinical information made available to health professionals and patients through social networks, capable of quickly and simply sharing general information about GTN [33,34]. The second is the possibility of caring for patients with GTN via telemedicine, either through end-to-end consultations with physicians (a GTN specialist remotely assisting patients with this disease alongside their primary care physician and local oncologist), or through remote consultations interspersed with face-to-face assistance [35,36]. Finally, the development and use of digital applications, especially those that use artificial intelligence, which can allow self-monitoring of results such as hCG and, therefore, optimize visits to the GTN-RC [37].

As the distance between the patient's residence and the GTN-RC is recognized as a risk factor for unfavorable outcomes, it is essential that these patients receive special supportive care. Primary care professionals must be prepared for early diagnosis and rapid referral of these cases to the RC. Specialists must also use psychosocial resources such as travel support to ensure access and maintenance of optimal healthcare for these patients to maximize the opportunity for cure.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.07.012.

Disclosures

The authors declare no conflicts of interest regarding the publication of this research.

Author contribution

The following authors were responsible for each of the stages of this study: Conceptualization: AB, RL, KME, NSH and RSB; Data curation: RL, AB, IM, CBS, EL, DY, EU, JMM and MV; Formal analysis: AB, RL, LGP, MB, KME, NSH and RSB; Funding acquisition: AB, RL, KME, NSH and RSB; Investigation: AB, RL, JAJ, JRF, KME, NSH and RSB; Methodology: AB, LGP, MB, KME, NSH and RSB, Project administration: AB, RL, KME, NSH and RSB; Resources: AB, RL, KME, NSH and RSB; Software: AB, RL, LGP and MB; Supervision: AB and RSB; Validation: AB, RL, LGP, MB, KME, NSH and RSB; Visualization: AB, KME, NSH and RSB; Writing - original draft: AB, RL, LGP, MB, KME, NSH and RSB; Writing - review & editing: all authors.

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