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ORIGINAL RESEARCH

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Symptomatic women experience long waits for endometrial cancer diagnosis and treatment in Brazil

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Abstract

The aim of this study was to assess the elapsed time for symptomatic women with endometrial carcinoma to achieve diagnosis and treatment and its impact on staging and survival. A cohort study was carried out with 430 women divided into in two groups: "Type I" (n = 289, endometrioid carcinoma grade 1 or 2); "Type II" (n = 141, nonendometrioid, endometrioid carcinoma grade 3, or carcinosarcoma). Clinical information, diagnostic methods, histology, staging, and time elapsed between symptoms-diagnosis-treatment were considered. Descriptive, survival, and regression analyses were performed. The symptom-to-diagnosis interval was 284 and 249 days in Types I and II ($p = 0.014$), with only 30% getting a diagnosis within 90 days. The diagnosis-to-treatment interval was shorter for Type II (100 *vs.* 123 days for Type I; $p = 0.001$). Only 12.5% of Type I and 22.7% of Type II started treatment within 60 days after diagnosis. There was no association between symptom-to-diagnosis interval and staging ($p = 0.377$). The symptom-to-treatment interval did not change the overall survival for Type I and had a paradoxical effect for Type II, with greater overall survival associated with a longer elapsed time ($p = 0.003$). Symptomatic Brazilian women with endometrial carcinomas showed very long wait times for diagnosis and treatment, and less than 23% started treatment within the regulatory period of 60 days. This critical situation does not exhibit any clear effect on cancer staging or overall survival, possibly counterbalanced by the faster care of patients with a poor prognosis, such as those with Type II endometrial carcinomas.

Keywords

Endometrial carcinoma; Staging; Services accessibility; Time-to-treat; Survival

1. Introduction

Malignant uterine neoplasms are the most common gynecological cancer and the sixth most common in women, with approximately 380,000 new cases per year [1]. Brazil had an estimated 6540 new cases in 2020 [2]. Carcinomas comprise 90–95% of cases, and the main risk factors are obesity, a sedentary lifestyle, and increased life expectancy [3, 4].

There are two subtypes of endometrial carcinomas, Types I and II, and this characterization is widely used in the initial planning of management [5]. Type I carcinomas account for 80% of cases, comprise endometrioid carcinoma grades 1 and 2, and are related to hyperestrogenism without progestin antagonism, a situation that can lead to endometrial hyperplasia [5–7]. Type II endometrial carcinomas encompass nonendometrioid histology, that is, papillary serous and clear-cell histology. Carcinosarcomas, undifferentiated carcinomas, and endometrioid carcinomas grade 3 are also included in this group, all with an aggressive pattern. This group is frequently associated with endometrial atrophy and mostly affects older women, and there is a higher proportion of diagnoses in advanced stages and with a worse prognosis [4–6].

Population screening methods to control uterine neoplasms have not shown advantages and most of these neoplasms have early symptoms, such as abnormal uterine bleeding, especially in postmenopausal women. A prompt investigation of these symptomatic women can lead to a diagnosis of malignant neoplasms in approximately 10%, usually in the early stages and with a high survival rate [7, 8].

In a previous study published by our group in 2021, a detailed profile of 1190 women with malignant uterine neoplasms was reported [9]. The analysis of a subgroup of 185 endometrioid carcinoma cases found that a long time elapsed between the onset of symptoms and starting treatment, averaging 376 days, and 82% of them waited more than 180 days before starting treatment. Unexpectedly, the long wait times did not worsen cancer staging or overall survival, although only 12% started treatment within 60 days of symptom onset, the local regulatory time frame [10]. A possible explanation was the relatively low aggressiveness of the endometrioid histology considered [9]. A similar lack of association has already been described for other neoplasms, and recent studies with

endometrial carcinomas have focused only on assessing the delay to start treatment, also with controversial results [11–14].

This study aimed to verify the time elapsed between the first symptoms until the diagnosis or treatment onset of women with type I or type II endometrial carcinomas, to evaluate its impact on the staging and overall survival, and to support strategies to shorten this process.

2. Materials and methods

A retrospective cohort study was carried out with a medical records review of 430 patients with uterine neoplasms treated between 2010 and 2018 in a regional cancer center under the Brazilian public health care system ("Sistema Unico de Saude—SUS"). The sample size calculation was based on a previous local study that showed a 75% overall survival rate at five years for endometrioid carcinoma grades 1 or 2 and 48% for endometrioid carcinoma grade 3 [9]. Fixing the Type I error at 5% and 80% of sample power, the required sample was 134 cases per prognostic group.

The institutional cancer registry was reviewed, and we selected 618 cases by code C.54 (malignant uterine neoplasia) from the International Classification of Diseases [15] and with origins from 42 municipalities that encompass 4.5 million people from the Administrative Region of Campinas (SP), Brazil. The flowchart of case selection is shown in Fig. 1, and it was considered whether there was information available in digital hospital medical records and, if necessary, physical records. First, the cohort with the less prevalent Type II neoplasms (nonendometrioid carcinomas, endometrioid carcinomas G3, and carcinosarcomas) was built. Cases selection started in the date April 2018 and continued backwards until the year 2010, keeping the different histology proportions similar to those previously reported [9] until the required number of cases was reached. The inclusion criteria were applied for all selected Type II cases when their medical records were reviewed: diagnosis confirmed by pathological report, treatment carried out at the institution, and symptomatic cases. The exclusion criteria were the origin of the cases outside of the considered region, a second synchronous neoplasia, incidental diagnosis, suspicion only by pelvic ultrasound or by Pap test, and cases with incomplete information or no follow-up. The excluded cases were replaced following the temporal sequence described above. In sequence, the same procedure was performed to build the cohort with Type I neoplasms (endometrial carcinomas G1 or G2), also controlling the histological grade proportion.

The Type I group had 289 cases and the Type II group had 141 cases. The data collected were categorized as follows: age (<50 years, 50–59, 60–69 and ≥70 years), signs and symptoms (abnormal uterine bleeding, vaginal discharge, pelvic pain, or abnormal clinical examination), diagnostic methods (curettage, hysteroscopy, endometrial biopsy, hysterectomy, peritoneal implants biopsy), histology (Type I or II), degree of differentiation (grades 1, 2 or 3) [16], International Federation of Gynecology and Obstetrics (FIGO)-2015 staging (I to IV) [17], elapsed times for diagnosis (up to 90 days, 91–180, 181–365, >365 days), time from diagnosis to treatment (up to 60 days, 61–90, >90 days), and total time from symptoms to treatment (up to 180 days, 181–365, >365 days). The

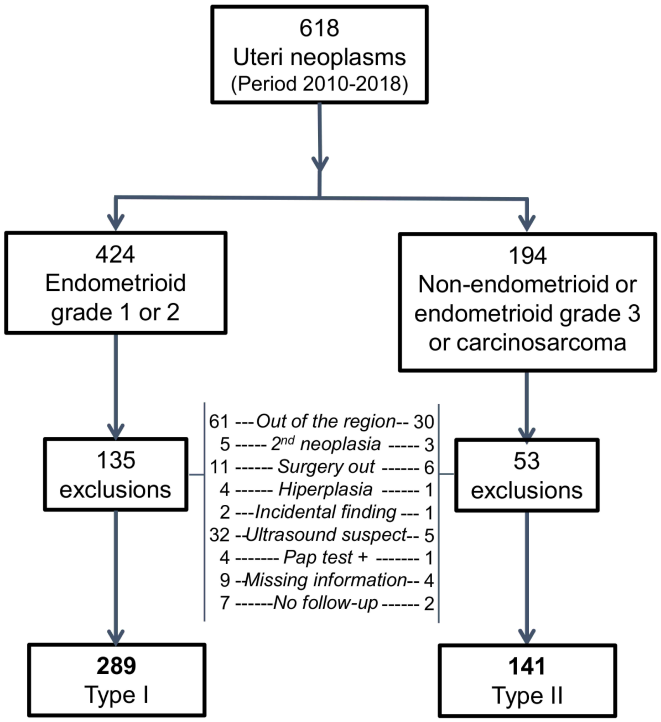

FIGURE 1. Flowchart of case selection. First, the cases for the Type II neoplasms were selected retrogradely, from April 2018 to 2010, keeping the different histology proportions similar to those previously reported [9] until the required sample number was reached. Similarly, the cohort with Type I neoplasms was built, also controlling the histological grade proportion. All selected cases had their medical records reviewed to confirm the diagnosis and treatment carried out at the institution. Only symptomatic cases were considered, and the exclusions were replaced following the temporal sequence.

duration of the symptoms considered before the diagnosis was calculated using information recorded in the hospital medical record, either in days, weeks (7 days) or months (30 days), and transformed into days. Several stratifications of time intervals were tested, but due to the long intervals found and with no correspondence in the current literature, intervals were defined using periods with some correlation with local practice or in correspondence with local legal guidelines. Overall survival started to count from the histopathological diagnosis until the last recorded contact or death. Statistical analysis used the chi-square, Fisher, or Mann-Whitney tests when appropriate, and survival analysis was performed with the Kaplan-Meier method and log-rank test. The univariate logistic regression analysis (Cox regression) for overall survival considered the variables age (as a continuous variable or age group), cancer staging, type of carcinoma, and the time intervals (symptom-diagnosis, diagnosis-treatment, and symptom-treatment). The median time and mean time intervals in days were calculated. The multivariate analysis considered only variables significant in univariate analysis. StatsDirect statistical software (Version 3.0, 2018, StatsDirect Ltd, Cambridge, UK) was used for statistics, and a p value < 0.05 was considered significant.

3. Results

The profiles of the Types I and II groups are described in Table 1, with a distribution by histological type similar to the institutional attendance [10], 68% of Type I and 32% of Type II carcinomas. Dilatation and curettage were the dominant diagnostic methods in both groups (45–47%), while hysteroscopy was more frequently applied in the Type I group (34.3% *vs.* 17%). Aspiration biopsy predominated in the Type II group (24.8% *vs.* 11.8%) ($p < 0.001$). The age group and cancer staging distribution showed a higher proportion of older ages and more advanced stages for the Type II group ($p = 0.010$), which could be expected. Symptoms of abnormal uterine bleeding were predominant, occurring in more than 95% of cases for both groups.

The symptom-diagnosis time interval had a median of 214 (7 to 1783) days and a mean of 284 days for Type I, and it was shorter for Type II, with median of 167 (13 to 2412) days and mean of 249 days ($p = 0.014$), and less than 30% of the women achieved at diagnosis within 90 days after the symptoms began. The diagnosis-treatment interval time was shorter for Type II, with a median of 92 days and a mean of 100 days, compared to a median of 115 days and a mean of 123 days for the Type I group ($p = 0.001$), and only 12.5%–22.7% of the women with endometrial carcinomas started treatment within 60 days after diagnosis. Considering the total time elapsed (symptom-treatment onset), there was a tendency for Type II cases to spend less time before starting treatment ($p = 0.004$), although this group also exhibited a higher proportion of cases where treatment could not be performed due to the advanced stage and/or early death of the patient (9.2% *vs.* 1%, $p < 0.001$; Table 2).

There was no association between the symptom-diagnosis time interval and cancer staging ($p = 0.377$). Stage I was 76.2% for Type I with an interval of 365 or more elapsed days, and Type II was 36.4% for Stage I with an interval of 181–365 elapsed days (Table 3). Paradoxically, the Type II cases exhibited a higher proportion of Stage IV (28.6%), which was associated with a shorter symptom-diagnosis time interval within 90 days. Comparing Type II cases at Stages I–II *vs.* Stages III ($p = 0.028$), or Stages I–II *vs.* Stage III–IV ($p = 0.010$) according to all intervals evaluated, there was a higher proportion of advanced stages diagnosed within 90 days, and this proportion progressively increased with shorter intervals, an unexpected and paradoxical effect (Table 3).

Assessing the association between the total symptom-treatment interval and the overall survival for all cases, the 5-year overall survival rate was lower for intervals up to 180 days (54%) compared to longer intervals (67%–73%, $p < 0.001$). Fig. 2 shows the overall survival analysis by group. Type I cases exhibited a high 5-year overall survival rate of 78–81%, similar to all intervals tested ($p = 0.878$, top chart). Type II cases exhibited a lower overall survival rate, but with another unexpected effect, where a shorter time of up to 180 elapsed days had a 5-year overall survival of 20%, lower than patients with a longer time before starting treatment (5-year overall survival of 50% for 365 or more elapsed days; $p = 0.003$, bottom chart).

In the regression analysis for overall survival by the type of endometrial carcinoma, death by Type II exhibited a hazard ratio (HR) of 5.33 (3.76–7.55) in univariate analysis and 2.06 (1.39–3.06) in multivariate analysis (*vs.* Type I, $p < 0.001$). The main finding in the multivariate analysis was a 44% decreased risk of death in the Type II group related to the diagnosis-treatment interval over 60 days (HR = 0.56 (0.35–0.91); $p = 0.020$), confirming the paradoxical effect.

4. Discussion

Symptomatic women with endometrial carcinoma in Brazil spent a long time waiting between the onset of symptoms until achieving a diagnosis and, subsequently, starting treatment. Less than 30% of them received the diagnosis within 90 days and less than 23% met the legal deadline to start treatment within 60 days after diagnosis [10]. Despite the long intervals observed, there was no significant association with worsening staging or overall survival, even when assessed by groups of histological types associated with different prognoses.

There was a predominance of abnormal uterine bleeding as the initial symptom reported by more than 95% of women with both types of carcinomas. Aspiration biopsies were rarely used for diagnoses, somewhat more in Type II (24% *vs.* 11% for Type I), perhaps due to the greater severity of symptoms at presentation requiring a more urgent diagnosis and treatment. The low proportion of aspiration biopsies used, a simple method for diagnosis of symptomatic women, although not accessible in the Brazilian Public Health System, can justify in part the long waiting time observed for the diagnosis, greater than eight months on average, when compared to the few weeks usually reported for other countries [11–14].

Overall, long periods spent to obtain the diagnosis, such as the average of 284 days observed for Type I and 249 days for Type II, could be expected to worsen the final staging, but this was not observed. The absence of this logical negative association may be related to the higher prevalence of Type I carcinomas, with a slow evolution and better prognosis. Other similar studies considered that some cases were not endometrial carcinoma when symptoms started but it then evolved into cancer during the wait [11, 12, 14]. Despite these explanations, it cannot be overlooked that 46%–56% of diagnoses were made more than six months after symptom onset, even though the cases evaluated came from a developed region of Brazil.

The Brazilian Health System does not have an effective guideline or recommendation for health professionals when presented with a symptomatic woman with a risk of endometrial cancer or even a precursor lesion. There is also no provision of diagnostic methods for cases with alarm signals, and these women wait for a test together with all other women of all ages and symptoms, and the system becomes inefficient at solving this situation promptly.

In a review of time intervals for the diagnosis of symptomatic women with endometrial carcinomas, we found two main divergences concerning those presented in this study that are probably related to health care access. First, there is a perception that the long waiting time for diagnosis is a problem that has been overcome when reviewing published studies from other countries. Second, most studies report results setting the

TABLE 1. Distribution of the 430 endometrial cancer cases studied by type according to age group, symptom, diagnostic method, and cancer stage.

Variable	Endometrial cancer				*p*
	Type I (n = 289)		Type II (n = 141)		
	n	%	n	%	
Age group (yr)					
<50	16	5.5	2	1.4	0.010
50–59	93	32.2	32	22.7	
60–69	110	38.1	57	40.4	
≥70	70	24.2	50	35.5	
Symptoms at diagnosis[a]					
Uterine abnormal bleeding	278	96.2	135	95.7	0.823
Vaginal discharge	3	1.0	0	0.0	
Pelvic pain	6	2.1	3	2.1	
Abnormal clinical exam	2	0.7	3	2.1	
Diagnostic method					
Dilatation and curettage	138	47.8	64	45.4	<0.001
Hysteroscopy	99	34.3	24	17.0	
Aspiration biopsy	34	11.8	35	24.8	
Biopsy of prolapsed uterine tumor or cervix	5	1.7	6	4.3	
Hysterectomy	13	4.5	10	7.1	
Carcinomatosis biopsy	0	0.0	2	1.4	
Stage[b]					
I	203	70.2	35	24.8	<0.001
II	35	12.1	22	15.6	
III	42	14.5	54	38.3	
IV	9	3.1	30	21.3	

[a] *Considered the main one.* [b] *Stage according to the FIGO-2015 system [17].*
Tests: Chi-square or Fisher.

TABLE 2. Type of symptomatic endometrial cancer and the time interval between diagnosis and starting treatment.

Time interval (d)	Endometrial cancer				*p*
	Type I (n = 289)		Type II (n = 141)		
	n	%	n	%	
Symptom to diagnosis					
Up to 90	58	20.1	42	29.8	0.111
91–180	68	23.5	33	23.4	
181–365	100	34.6	44	31.2	
>365	63	21.8	22	15.6	
Median (Min–Max)	214 (7–1783)		167 (13–2412)		
Mean	284		249		0.014
Diagnosis to treatment onset					
Up to 60	36	12.5	32	22.7	<0.001
61–90	48	16.6	31	22.0	
>90	202	69.9	65	46.1	
Not applicable	3	1.0	13	9.2	<0.001
Median (Min–Max)	115 (1–534)		92 (1–326)		
Mean	123		100		0.001
Symptom to treatment onset					
Up to 180	52	18.0	41	29.1	0.004
181–365	102	35.3	44	31.2	
>365	132	45.7	43	30.5	
Not applicable	3	1.0	13	9.2	<0.001
Median (Min–Max)	344 (59–1870)		271 (30–2572)		
Mean	408		353		0.001

[a] *Treatment not given.*
Tests: Chi-square or Fisher, and Mann-Whitney for mean.

TABLE 3. Endometrial cancer staging according to cancer type and the time elapsed (days) from symptoms to diagnosis.

Stage[a]	Symptom to diagnosis interval by type (n = 430)															
	Up to 90 days				91 to 180 days				181 to 365 days				>365 days			
	Type I		Type II		Type I		Type II		Type I		Type II		Type I		Type II	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
I	36	62.1	6	14.3	48	70.6	6	18.2	71	71.0	16	36.4	48	76.2	7	31.8
II	10	17.2	4	9.5	6	8.8	5	15.2	12	12.0	7	15.9	7	11.1	6	27.3
III	10	17.2	20	47.6	9	13.2	15	45.5	16	16.0	12	27.3	7	11.1	7	31.8
IV	2	3.4	12	28.6	5	7.4	7	21.2	1	1.0	9	20.5	1	1.6	2	9.1
Total	58	100	42	100	68	100	33	100	100	100	44	100	63	100	22	100

[a] *Stage according to the FIGO-2015 system [17].*
Type I: endometrioid carcinomas grade 1 or 2.
Type II: nonendometrioid or endometrioid grade 3 carcinomas and carcinosarcomas.
All cases: p = 0.377 (Fisher test).
Type I Stage I–II vs. III–IV: p = 0.374 (Chi-square test).
Type II Stage I–II vs. III: p = 0.028; and Stage I–II vs. III–IV: p = 0.010 (Fisher test).

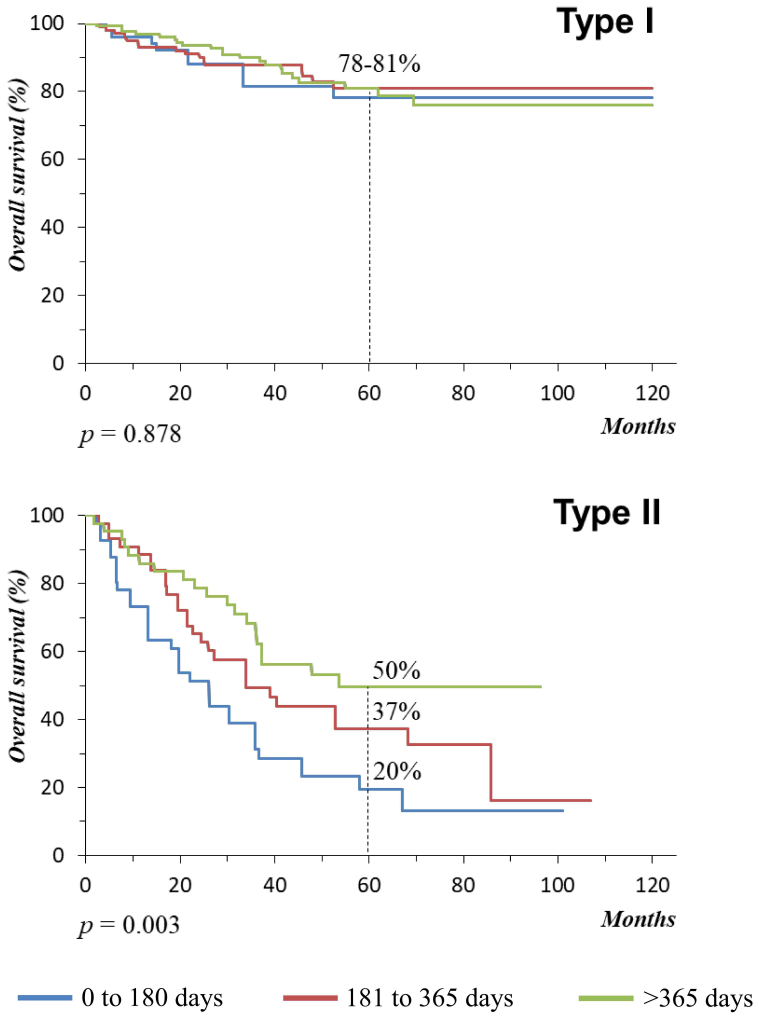

FIGURE 2. Overall survival by the type of endometrial carcinoma according to the elapsed symptom-treatment onset time. Type I cases exhibited a high 5-year overall survival rate of 78–81%, similar to all intervals tested ($p = 0.878$, top chart). Type II cases exhibited a lower overall survival rate, with a shorter time of up to 180 elapsed days (survival of 20%), lower than patients with a longer time before starting treatment (50% for 365 or more elapsed days; $p = 0.003$, bottom chart). Kaplan-Meier method and log-rank test.

waiting limit to a few weeks, usually four to eight weeks [11–14]. Countries with more resources have already overcome all of these issues, including self-care education for women to recognize the need for evaluation in the face of symptoms such as postmenopausal vaginal bleeding and the certainty that a diagnosis will be reached quickly and clearly. In these places, the current concern is to shorten the time to the start of cancer treatment as much as possible and improve its quality, aiming to obtain better results [12–14].

Expanding the literature review, we found a North American study from 1995, which reported waiting periods of three to six months, similar to our results. Interestingly, this study also did not find a significant correlation between the time spent between symptoms and diagnosis and the prognosis. The authors noted that 50% of cases waited more than three months for a diagnosis and 27% waited more than six months [11]. Comparatively, our results come from a region with the best health system offered to the population, and it still found extremely long waiting times, an issue that has already been corrected in other countries [12–14].

However, the second period analyzed, the time elapsed between diagnosis and when treatment starts, is still widely studied for several neoplasms, including uterine neoplasms. This interval is considered a reference to measure the capacity of assessment and quality of oncology care [12–14]. Studies in this field recommend a time limit for starting treatment ranging from four to six weeks after diagnosis, and this gap is not associated with worsening postoperative staging or overall survival [12, 13]. In the present study, the mean time elapsed was greater than 100 days, more than double the published limits [11–14, 18].

Despite the differences in the time intervals from other studies, our results indicate that the elapsed time did not make a significant difference in the overall survival for Type I cases, which remained high for any interval of time analyzed. Paradoxically, the multivariate regression analysis for overall survival of Type II cases showed an association between shorter time intervals to start treatment (faster onset) and an increased risk of death. Similar results have already been reported in other studies and, possibly, are related to greater severity and a faster and more impactful evolution, resulting in acceleration of the management process and starting treatment in less time [11, 13]. Even so, due to the greater aggressiveness of Type II neoplasms, treatments cannot reverse the outcome in a representative proportion of women.

Our service, as the only Public Cancer Center for a vast region, has the particularity of assisting a higher proportion of Type II cases than expected (32% *vs.* 20%), while Type I cases are manageable with surgeries such as total hysterectomy with bilateral adnexectomy, accessible in other locations. Although this service pattern may have influenced the paradoxical effect observed for Type II cases, in a previous study with 185 Type I symptomatic women, this paradoxical effect was not observed, with long waiting periods and, likewise, no association with staging or survival [9].

AlHilli and colleagues [13] studied 284,499 cases of endometrial carcinomas in an American registry system from 2004–2013, with 83% being Type I and 17% being Type II. A median of 26–27 days was found between diagnosis and treatment, and the detailed analysis also showed a paradoxical effect: for Type II, with better overall survival for women who took more than six months to start treatment. In contrast, for Type I, a delay greater than six weeks was associated with worse overall survival only for early-stage endometrial carcinoma (I and II).

Our results confirm a similar pattern, with Type II cases presenting at advanced stages in 75%, with survival curves suggesting a rapid evolution and an important finding that 9.2% of cases died before receiving any treatment. In addition, the Type II cases that did not fit this aggressive profile tend to show an evolution similar to the Type I cases. These observations make clear the need to expand the use of biomarkers or genetic studies, which are still not very accessible, to advance prognostic discrimination.

Regardless, a postmenopausal woman with abnormal uterine bleeding requires prompt assessment in primary and secondary health care to rule out the 20% possibility of cancer or precursor lesions [12, 14, 18–20]. There is a current progressive increase in the incidence of endometrial carcinomas, mainly Type I, and the health system needs to adapt and plan how to act in response [18–20]. The Brazilian legal limit of 60 days of waiting to start cancer treatment from diagnosis has existed since 2012 [10], and our results point to minimal compliance with the law, 12% for Type I cases and 22% for Type II, the more severe cases. The current perspective, post pandemic, is that the scenario will worsen [21].

The limitations of this study are related to the retrospective pattern from a single center and the possible lower accuracy of information recorded in the medical record related to the duration of symptoms. There was observed a great variability in the medians of the intervals studied, and cases with longer duration may have influenced the high mean intervals times found. The long waits for diagnosis in our daily practice are real, became worse after the pandemic, and after two years, no changes were noted in this scenario. However, this study was carried out in a cancer center with an electronic system and recorded high-quality information used by official surveillance agencies. Our regional hospital has a multiprofessional team that cares for women with gynecological neoplasms following standardized guidelines for staging and treatment.

As a relevant institution of the Brazilian Public Health System taking care of complex cases and a center for training health professionals, we must take the lead and make changes. Our study, even generating evidence of relative impact, is part of a strategy to provide information based on real life to discuss the necessary transformations. Planning an optimal care flowchart and educational actions could help women recognize postmenopausal vaginal bleeding as a warning sign and seek a health care unit. First, the health care system would need to be prepared to welcome and screen any woman with warning signs in an early gynecological consultation [19], shortening the time until a diagnosis. The use of aspiration biopsy devices by trained professionals and guidance provided by a predefined flowchart is crucial. These measures should reduce the number of cases of advanced endometrial carcinomas, saving costs for expanding the treatment offered.

5. Conclusions

Symptomatic women with endometrial carcinomas showed very long wait times for diagnosis and treatment with less than 30% achieving a diagnosis within 90 days of symptom onset, and less than 23% of cases starting treatment within the regulatory period of 60 days. The long intervals observed did not have a clear effect on staging or overall survival, possibly counterbalanced by the faster care of Type II cases, with a poor prognosis and advanced stage.

AVAILABILITY OF DATA AND MATERIALS

The data related to this research is available at https://data.mendeley.com/datasets/27mrkw7j4b/1 (DOI: 10.17632/27mrkw7j4b.1).

AUTHOR CONTRIBUTIONS

EC and JTeixeira—designed the research study, wrote the manuscript. EC, JTorres, DY, CP, LC and JTeixeira—performed the research. DY and LC—provided help and advice on methodology. EC, JTorres and JTeixeira—analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was previously approved by the Research Ethics Committee of the University of Campinas (Approval 4.675.573, 09 March 2021), which waived the need to apply an informed consent form.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. JTeixeira is serving as one of the Editorial Board members/Guest editors of this journal. We declare that JTeixeira had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to EH.

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