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ORIGINAL ARTICLE / *ARTIGO ORIGINAL*

Survival and prognostic factors in patients with Non-Small Cell Lung Cancer treated in private health care

Sobrevida e fatores prognósticos em pacientes com câncer de pulmão de células não pequenas assistidos na saúde suplementar

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ABSTRACT: ***Introduction:*** Outcomes data on Non-Small Cell Lung Cancer (NSCLC) are scarce with regard to the private health care in Brazil. The aim of this study was to describe the characteristics, treatments performed, and the survival of patients with NSCLC in a Brazilian private oncologic institution. ***Methods:*** Medical charts from patients treated between 1998 and 2010 were reviewed, and data were transferred to a clinical research form. Long-term follow-up and survival estimates were enabled through active surveillance. ***Results:*** Five hundred sixty-six patients were included, and median age was 65 years. Most patients were diagnosed in advanced stages (79.6% III/IV). The overall survival was 19.0 months (95%CI 16.2 – 21.8). The median survival was 99.7, 32.5, 20.2, and 13.3 months for stages I, II, III, and IV, respectively ($p < 0.0001$). Among patients receiving palliative chemotherapy, the median survival was 12.2 months (95%CI 10.0 – 14.4). ***Conclusions:*** The outcomes described are favorably similar to the current literature from developed countries. Besides the better access to health care in the private insurance scenario, most patients are still diagnosed in late stages.

Keywords: Lung neoplasms. Epidemiology. Supplemental health. Neoplasm staging. Survival analysis. Treatment.

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RESUMO: ***Introdução:*** Dados de desfechos em câncer de pulmão de células não pequenas (CPCNP) são escassos no contexto da saúde suplementar no Brasil. O objetivo deste estudo foi descrever as características, tratamentos realizados e a sobrevida desses pacientes em uma instituição oncológica privada brasileira. ***Métodos:*** Foram revisados os prontuários de pacientes atendidos entre 1998 e 2010 com diagnóstico de CPCNP. Os dados foram transferidos para uma ficha clínica individual e posteriormente analisados. Pacientes ou familiares foram contatados a fim de otimizar o seguimento e a estimativa da sobrevida. ***Resultados:*** Foram incluídos 566 pacientes, com idade mediana de 65 anos. Predominaram os diagnósticos em estádios avançados (79,6% III/IV). A sobrevida mediana foi de 19,0 meses (IC95% 16,2 – 21,8), sendo de 99,7, 32,5, 20,2 e de 13,3 meses nos estádios I, II, III e IV, respectivamente ($p < 0,0001$). Entre os pacientes que receberam quimioterapia paliativa, a sobrevida mediana foi de 12,2 meses (IC95% 10,0 – 14.4). ***Conclusões:*** Os desfechos encontrados se assemelham aos de países desenvolvidos. Apesar do maior acesso médico em pacientes com cobertura de planos de saúde, a maioria dos diagnósticos ocorre tardiamente.

Palavras-chave: Neoplasias pulmonares. Epidemiologia. Saúde suplementar. Estadiamento de neoplasias. Análise de sobrevida. Tratamento.

INTRODUCTION

Lung cancer is the malignant neoplasm of highest incidence worldwide[1]. According to data from GLOBOCAN[1], 1,095,200 new cases were estimated among men and 513,600 among women in 2008. In developed countries, this incidence has been declining among men and remained stable among women, reflecting the reduction in the rates of smoking among males[2]. It is also the leading cause of cancer-related death worldwide, with an estimated 951,000 deaths in males and 427,400 in females in 2008[1]. These numbers are greater than the sum of deaths from breast, prostate and colon cancer, and represent about 18% of all cancer deaths[1].

In Brazil, lung cancer is the second most frequent cancer in men and fourth in women[3], with 17,210 estimated new cases among men and 10,110 among women in 2012[3]. According to data from population-based registries[4], the estimated risk between 2001 and 2005 was 29.08 new cases per 100,000 men and 11.49 per 100,000 women, taking the city of São Paulo as reference. It is still the leading cause of cancer-related death among men and the second leading among women, with 11,315 estimated deaths in males and 4,915 in females in 2003[5].

Unlike the U.S. data, the incidence and mortality in Brazil follow an upward curve, with progressively higher diagnostic and mortality rates. It is noteworthy that non-small cell lung cancer (NSCLC), the subject of this article, represents about 80% of

cases and mainly comprises the adenocarcinoma, squamous cell carcinoma and large cell carcinoma subtypes[6].

Most advances in the treatment of lung cancer came from international cooperative groups, which indicates the need to validate this information locally. Furthermore, data on outcomes in NSCLC were little explored in the context of private healthcare in Brazil so far. For this reason, we proposed a retrospective study in order to evaluate patients served at a Brazilian private health institution for a period of 12 years. This information is essential for the understanding of local outcomes and may guide the best allocation of resources in the medium term.

MATERIALS AND METHODS

DESIGN

This is a retrospective study conducted by evaluating medical records of patients diagnosed with NSCLC treated in a Brazilian private health institution. For data collection, a clinical form that included characteristics such as age, performance status (PS), presence and degree of weight loss, stage of disease at diagnosis, date of diagnosis, histological type, primary surgery (if performed) and current disease situation, was standardized.

PS was categorized from 0 to 4, according to the scale from the Eastern Cooperative Oncology Group (ECOG)[7]. Fully active and asymptomatic patients were categorized as PS 0, while those with minimal symptoms were defined as PS 1. PS 2 was used to define patients incapable of performing work activities and who remained seated or laid down for less than half the day. Bed-ridden patients or those who remained seated for more than half of the day, dependent on help for personal care activities, were defined as PS 3. PS 4 comprised completely incapable of self-care, bed-ridden patients.

The staging was defined according to the sixth edition of the American Joint Committee on Cancer (AJCC)[8]. Patients with malignant pleural or pericardial effusion (the old "wet" stage IIIB) were included in the category of patients in stage IV. Regarding chemotherapy, the drugs used in each situation, the date of the cycles and the date of death or the last visit at the institution were recorded. Among patients treated with palliative chemotherapy, details of the first palliative treatment (first line) and, when present, of the subsequent systemic therapies (second line), were verified. When patients did not present a frequent follow-up or when the date of death was not found in medical records, patients or relatives were contacted by telephone to update follow-up information or to verify the date of death. No searches in the Mortality Information System (SIM) were performed. The data collected were stored in spreadsheets in the Access software, and analyzed using SPSS 17.0 (SPSS Inc., California, USA).

OBJECTIVES AND VARIABLES

The primary objective of this study was to describe the basic characteristics and the treatments carried out. As secondary objectives, we analyzed the overall survival rate (OSR) of patients stratified by tumor stage, and, in the subgroup of patients treated with palliative chemotherapy, estimated survival according to the presence of known prognostic factors.

STUDY POPULATION

Patients with NSCLC confirmed by pathological examination (histology or cytology) receiving care at the Integrated Oncology Clinics Group (COI) between December 1998 and June 2010 were included. The exclusion criteria defined was the presence of other concurrent malignancies within five years preceding the diagnosis of lung cancer, except non-melanoma skin cancer and cervical cancer with more than three years of control. Also ineligible were patients who had received prior treatment for lung cancer at other institutions (public or private). These criteria are commonly used in the literature, and allow the reduction of selection biases that could impact the prognosis. The results are presented in two sections, the first involving the entire study cohort represented by 566 patients, and the second comprising the subcohort treated with palliative chemotherapy, that included 339 patients.

STATISTICAL ANALYSIS

The distribution of the OSR was estimated by the Kaplan-Meier method and defined as the time interval between diagnosis and death. Among patients undergoing palliative chemotherapy, survival was estimated as the interval between the start of treatment and death. Follow-up time was calculated from the medians of the intervals. The variable of interest was death from any cause, including lung cancer. For live patients or those who lost follow-up, data were censored at the date of last contact. Analysis of variables for survival was performed using the log-rank method, considering the following variables of interest: age, sex, PS, weight loss, smoking, histology and tumor stage. Multivariate analysis was not performed due to the primarily descriptive nature proposed here. The curves of overall survival rates and those for which more marked differences were observed were presented graphically. Statistical significance was indicated by p-value ≤ 0.05.

ETHICAL ASPECTS

This study was approved by the local research ethics committee and the non-use of an informed consent form was properly justified. The ethical aspects are in accordance with the Resolution CNS 196/96 (DO. No. 201, October 16, 1996) and its complementary resolutions.

RESULTS

TOTAL COHORT

A total of 566 patients were included, with a median age of 65 years (ranging from 27 to 92). The majority were male (59.4%), of which 83.6% were smokers or ex-smokers. The most common histological type was adenocarcinoma, defined in 326 patients (59.1%), followed by squamous cell carcinoma in 110 cases (19.9%). Two hundred and eighty-eight patients (52.9%) were diagnosed with stage IV, while 145 (26.7%) with stage III, 38 (7.0%) in stage II and 73 (13.4%) in stage I. The basic characteristics are summarized in Table 1. One hundred and fifty-five patients (28.1%) underwent surgery with curative intent. Of these, 67 (43.2%) were treated with adjuvant chemotherapy, and 23 (14.8%) with neoadjuvant. Palliative chemotherapy was used in 339 patients (59.9%), of which 166 (29.3%) also received second line chemotherapy. Two hundred eighty-seven patients (50.7%) were treated with radiotherapy at some time during the course of the disease, with the majority (188 cases) being carried out in palliation. Treatment data are presented in Table 2.

With a median follow-up of 12.8 months, median OSR was 19.0 months (95%CI 16.2 – 21.8). The median OSRs per stage were 99.7 months (95%CI 36.0 – 163.3), 32.5 months (95%CI = could not estimate), 20.2 months (95%CI 15.4 – 24.9) and 13.3 months (95%CI 11.4 – 15.3) in stages I, II, III and IV, respectively ($p < 0.0001$). The estimated OSR at 2 years was 88.9%, 61.9%, 43.9% and 26.6% in stages I, II, III and IV, respectively (Table 3 and Figure 1). Female patients also had greater survival rates ($p = 0.002$), as well as those with better PS ($p < 0.001$), no weight loss ($p < 0.001$) and no history of smoking ($p = 0.048$).

PATIENTS TREATED WITH PALLIATIVE CHEMOTHERAPY

Among patients treated with palliative chemotherapy (n = 339), the majority (236 patients) presented advanced stages at diagnosis (72.4%), while 90 (27.6%) were treated after relapse (Table 1). Ninety patients (54.5%) had weight loss greater than or equal to 10% of body weight and 205 (89.1%) had PS 0-1. One hundred and sixty-six patients (48.9%) received second-line therapy and 57 (34.3%) received third line. Most patients received treatment based on platinum in the first line, with the combination with paclitaxel

Table 1. Baseline characteristics of patients evaluated between 1998 and 2010.

Characteristics	Total cohort (n = 566)	Palliative Treatment (n = 339)
	n (%)	n (%)
Median age (variation)	65 (27 – 92)	64 (27 – 86)
Gender		
Male	336 (59.4)	200 (59.0)
Female	230 (40.6)	139 (41.0)
Smoking		
Smokers/Ex-smokers	427 (83.6)	256 (82.6)
Non-smokers	84 (16.4)	54 (17.4)
Performance status		
0	149 (39.6)	80 (34.8)
1	180 (47.9)	125 (54.3)
2	31 (8.3)	23 (10.0)
3	13 (3.4)	2 (0.9)
4	3 (0.8)	–
Weight loss		
Yes	152 (55.7)	90 (54.5)
No	121 (44.3)	75 (45.5)
Histology		
Adenocarcinoma	326 (59.1)	204 (62.2)
Squamous-cell carcinoma	110 (19.9)	61 (18.6)
Others	116 (21.0)	63 (19.2)
Stage		
I	73 (13.4)	18 (5.5)
II	38 (7.0)	14 (4.3)
III	145 (26.7)	58 (17.8)
IV	288 (52.9)	236 (72.4)

Table 2. Treatment characteristics in patients evaluated between 1998 and 2010 (n = 566).

Type of treatment	n (%)
Surgery with curative intent	155 (28.1)
Adjuvant chemotherapy	67 (11.8)
Neoadjuvant chemotherapy	23 (4.1)
Palliative chemotherapy	339 (59.9)
Radiotherapy*	287 (50.7)

*At any time during treatment.

being the most common (31.0%), followed by combination with pemetrexed (20.9%) and gemcitabine (17.4%).

With a median follow-up of 12.0 months, the median OSR was 12.2 months (95%CI 10.0 – 14.4). Survival was significantly higher among patients without weight loss (median 13.1 [95%CI 8.7 – 17.6] versus 8.4 months [95%CI 7.0 – 9.7], p = 0.038), no history of smoking (median 18.2 [95%CI 12.7 – 23.6] versus 11.6 months [95%CI 9.3 – 13.9], p = 0.007) and with adenocarcinoma histology (median 13,5 [95%CI 11.2 – 15.8] versus 9.7 months [95%CI 6.8 – 12.5] for squamous histology and 9.2 months [95%CI 5.0 – 13.3] for other histological subtypes, p = 0.002). Moreover, there was no difference in survival rates according to age (p = 0.571), gender (p = 0.093), Performance Status (p = 0.099) and stage (p = 0.64) (Table 4 and Figure 2).

DISCUSSION

The importance of prospective and retrospective records in lung cancer has been widely demonstrated in international examples[9-11] and are essential today for a critical and responsible analysis of the incorporation of new strategies and technologies in these countries. In Brazil, these tools gain additional importance with the need to demonstrate the true impact of these incorporations, as well as requiring cost-effectiveness and budget impact locally. In this project, 566 cases of NSCLC treated in a Brazilian private health institution were reviewed. This information will compose the basis for future comparisons, especially with the introduction of new technologies and the incorporation of the seventh AJCC classification for staging.

Among the strengths of this study, we can highlight the long follow-up period and the relatively high number of patients. Furthermore, the use of an objective outcome such as OSR allowed a better access to data. As mentioned in Materials and Methods, active search by telephone was performed to optimize the tracking of information on follow-up and

Table 3. Analysis of prognostic factors in the total cohort (n = 566).

Variables	OSR at 2 years (%)	Median OSR (months)	95%CI	p-value
Age				0.082
< 65 years	47.1	20.2	14.9 – 25.4	
≥ 65 years	40.0	18.4	15.9 – 20.8	
Gender				0.002
Male	39.5	17.5	14.4 – 20.6	
Female	49.9	23.9	14.8 – 33.0	
Performance Status				< 0.001
0	60.7	36.5	21.9 – 51.1	
1	30.5	15.2	12.3 – 18.1	
2	33.7	8.9	4.2 – 13.5	
3	18.5	9.4	0 – 23.5	
4	0	2.4	–	
Weight loss				< 0.001
Yes	25.4	12.5	9.4 – 15.5	
No	53.1	28.1	16.0 – 40.2	
Smoking				0.048
Yes	41.5	18.0	15.6 – 20.3	
No	51.0	26.9	16.7 – 37.0	
Histology				0.367
Adenocarcinoma	46.3	20.2	15.9 – 24.4	
SCC	42.3	18.2	12.7 – 23.7	
Others	37.2	17.4	11.0 – 23.8	
Stage				< 0.0001
I	88.9	99.7	36.0 – 163.3	
II	61.9	32.5	–	
III	43.9	20.2	15.4 – 24.9	
IV	26.6	13.3	11.4 – 15.3	

OSR: overall survival rate; SCC: squamous-cell carcinoma.

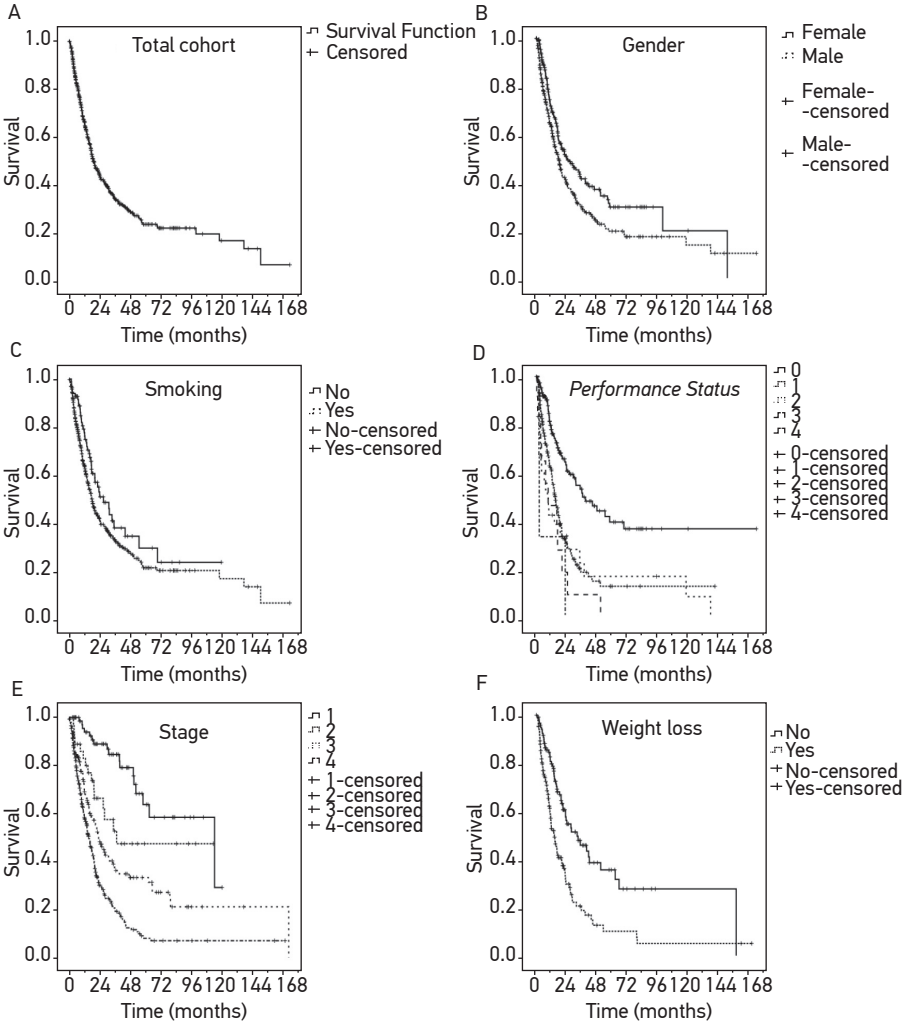

Figure 1. Survival curves in patients with Non-Small Cell Lung Cancer treated with palliative chemotherapy between 1998 and 2010 (A) according to gender (B), smoking status (C), Performance Status (D), staging (E), and weight loss (F) (n = 566).

death. We also decided to exclude patients who started treatment at other institutions. With that, we reduce the possibility of selection biases, since the information on patients with worse prognoses could be ignored. Furthermore, the data presented here indicate outcomes that are representative of daily practice, in contradiction to the environment of clinical trials, characterized by a restricted inclusion of patients[12]. Moreover, the long time of entry of patients in the study may consist of a limitation, since there has been progress

Table 4. Analysis of prognostic factors in patients treated with palliative chemotherapy (n = 339).

Variables	OSR at 1 year (%)	Median OSR (months)	95%CI	p-value
Age				0.571
< 65 years	49.0	11.7	8.3 – 15.2	
≥ 65 years	51.6	12.9	9.6 – 16.2	
Gender				0.093
Male	49.1	11.7	8.9 – 14.5	
Female	52.7	13.1	9.8 – 16.4	
Performance Status				0.099
0	59.6	15.1	11.0 – 19.3	
1	47.2	11.4	7.9 – 14.9	
2/3	37.6	8.4	2.3 – 14.4	
Weight loss				0.038
Yes	38.4	8.4	7.0 – 9.7	
No	53.4	13.1	8.7 – 17.6	
Smoking				0.007
Yes	48.6	11.6	9.3 – 13.9	
No	67.0	18.2	12.7 – 23.6	
Histology				0.002
Adenocarcinoma	55.9	13.5	11.2 – 15.8	
SCC	43.0	9.7	6.8 – 12.5	
Others	36.1	9.2	5.0 – 13.3	
Stage				0.64
Metastatic	52.4	12.8	10.5 – 15.0	
Recurrent	44.0	9.7	5.6 – 13.8	

OSR: overall survival rate; SCC: squamous-cell carcinoma.

in diagnosis and treatment methods over the years, and perhaps not all patients have had equal access. Another weakness was the non-performance of search on SIM to confirm the date of death in this cohort.

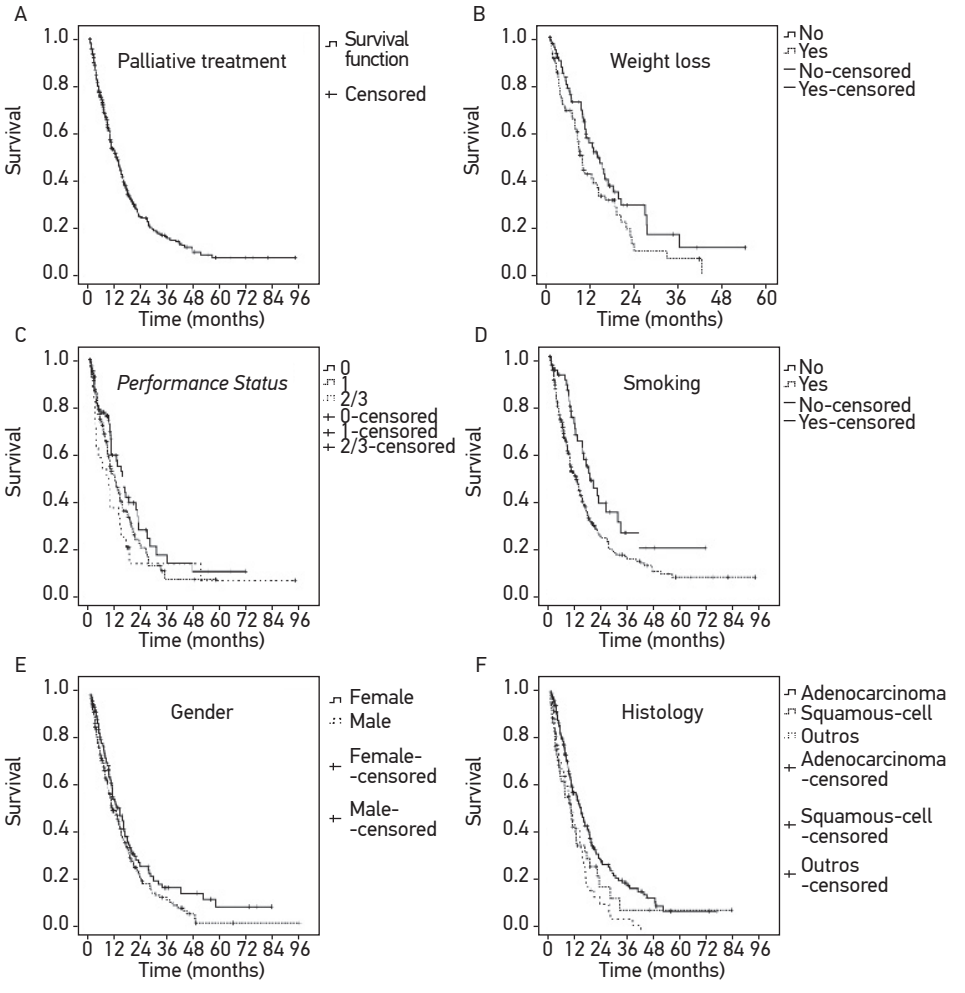

Figure 2. Survival curves in patients with Non-Small Cell Lung Cancer treated with palliative chemotherapy between 1998 and 2010 (A) according to weight loss (B), performance status (C), smoking status (D), gender (E), and histologic subtype (F) (n = 339).

In our survey, we found clinical characteristics and therapeutic strategies that are approximate to those described in developed countries. As an example, the median age found (65 years), the percentage of male patients (59.4%) and the percentage of nonsmokers (16.4%) are close to the data registered in countries like England and Canada[9,10]. Still, this study found a predominance of adenocarcinoma (59.1%), which is consistent with the

literature. The high rate of patients diagnosed at advanced stages (79.6% in stage III/IV) is a fact that raises interest. Although consistent with the literature, one would expect a higher proportion of patients with early diagnosis in the context of private health. As a rule, these patients have faster access to health care, as well as to examinations, compared to patients without health insurance coverage. This information also supports the need to prioritize primary prevention measures — such as anti-smoking campaigns — as well as early detection strategies.

The treatment used is in line with data from international registries. In fact, 155 patients analyzed in this study underwent surgery with curative intent, of which 67 (43.2%) received adjuvant chemotherapy. These proportions are similar to the Canadian data[10] (Ontario province), where the proportion of patients treated with adjuvant treatment was 31% after 2004. Accordingly, the median OSR among the patients studied here was 19.0 months; therefore, it is in live with data from developed countries[9,10]. We also found a significant difference in survival rates according to stage at diagnosis. At this point, we emphasize the higher OSR of patients in stage I, which allows the projection of the impact of early screening programs that significantly increase the proportion of patients diagnosed at this stage. With the increasing cost of treatment of advanced lung cancer, effective strategies that lead to early detection — as imaging or biomarkers[13,14] — and to the reduction of the proportion of patients who develop metastatic disease can greatly reduce the expense of the health system intended to the treatment of this disease. Ultimately, this would allow ever-greater resources to be allocated for use in early diagnosis, prevention and support programs.

In this study, we also explored the characteristics and outcomes of patients undergoing palliative chemotherapy. Notably, the median survival rate reported (12.2 months) resembles that of developed countries and large clinical trials[9,15,16]. As an example, the median survival rate reported in a clinical trial comparing two contemporary chemotherapy regimens was 10.3 months[16]. In our study, 48.9% of patients received second-line therapy, which approximates the proportion of first-line therapy mentioned in clinical trials[17]. On the other hand, the survival rate is much higher than that of public health services in Brazil, where median survival rates in the range of 7.1 months were described[18]. In this sense, some factors may have interfered, among which stands out the time taken for diagnosis and the beginning of the palliative treatment. That is, it is possible that patients treated in private health services have faster access to diagnosis and that survival rates are distorted by the early beginning of treatment. In other words, the anticipation of diagnosis could extend the time of observation, but it would have no impact on the outcome of death, which would constitute a time bias. However, we must mention that there are marked differences in the therapy used in these two situations. Unlike surveys in public services, the patients in this study often used new generation agents, and had greater access to subsequent lines of chemotherapy, interventions that are known to prolong survival[16,19].

CONCLUSION

Patients treated in a Brazilian private oncologic institution had characteristics and outcomes similar to those described in developed countries. A high proportion of patients diagnosed at advanced stages raises interest to the need of prioritizing measures for primary prevention (such as tobacco control campaigns), as well as new strategies for early diagnosis. The survival rates of patients treated with palliative chemotherapy is similar in data from international literature and shows to be superior to national public health services.

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