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Factors influencing treatment selection and survival in advanced lung cancer

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ABSTRACT

Purpose Despite numerous breakthrough therapies, inoperable lung cancer still places a heavy burden on patients who might not be candidates for chemotherapy. To identify potential candidates for the newly emerging immunotherapy-based treatment paradigms, we explored the clinical and biologic factors affecting treatment decisions.

Methods We retrospectively reviewed the records of patients diagnosed at our university-affiliated cancer centre between 1 January 2011 and 31 December 2013. Patient demographics, systemic treatment, and survival were examined.

Results During the 3-year study period, 683 patients fitting the inclusion criteria were identified. First-line therapy was administered in 49.5% of patients; only 22.4% received further lines of therapy. The main reasons for withholding therapy were poor performance status [PS (43.2%)], rapidly deteriorating PS (31.9%), patient refusal of therapy (20.9%), and associated comorbidities (4%). Older age, the presence of brain metastasis at diagnosis, and non-small-cell histology were also associated with therapeutic restraint. Oncology referrals were infrequent in patients who did not receive therapy (32.2%). Older patients and those with a poor PS experienced superior survival when treatment was administered (hazard ratio: 0.25; 95% confidence interval: 0.16 to 0.38; and hazard ratio: 0.44; 95% confidence interval: 0.23 to 0.87 respectively; $p < 0.001$).

Conclusions Advanced lung cancer still poses a therapeutic challenge, with a high proportion of patients being deemed unfit for therapy. This issue cannot be resolved until appropriate measures are taken to ensure the inclusion of older patients and those with a relatively poor PS in large clinical trials. Immunotherapy might be interesting in this setting, given that it appears to be more tolerable. Another consequential undertaking would be the deployment of strategies to reduce wait times during the diagnostic process for patients with a high index of suspicion for lung cancer.

Key Words Advanced lung cancer, non-small-cell lung cancer, small-cell lung cancer, treatment selection, treatment decisions

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INTRODUCTION

Medical oncology has witnessed the discovery of multiple breakthrough therapies since the early 2000s, and yet cancer still ranks 2nd in terms of overall population mortality[1]. Lung cancer, being the 2nd most common cancer in men and women, accounts for the most cancer-related fatalities[1]. Unfortunately, more than two thirds of patients are diagnosed at an advanced stage, which precludes referral to curative-intent surgery[2]. Such patients could be candidates for standard therapeutic approaches, which usually consist of chemotherapy or, in select cases in which predictive biomarkers are identified, targeted therapy[3,4]. Alternatively, patients might be referred to palliative care services where therapeutic interventions are exclusively aimed at symptom palliation.

In concert with the guiding medical principle *primum non nocere*, the potential benefits of any therapeutic approach must be carefully weighed against its potential toxicities, which can be considerable when chemotherapy is involved. Prognostication is the essential element affecting treatment selection in patients with advanced lung cancer. However, practitioners are often inaccurate and can be overly optimistic when predicting survival in cancer

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patients, thus leading to excessive treatments[5–8]. Conversely, clinicians with limited experience in managing cancer patients might be prone to underestimating prognosis and might subsequently withhold life-prolonging treatments[5].

The administration of chemotherapy is mostly reserved for "medically fit" patients, and PS, a subjective evaluation used by clinicians, appears to be the most widely accepted measure of "fitness"[9]. Because large clinical trials usually exclude patients with a poor Eastern Cooperative Oncology Group (ECOG) PS, the optimal approach for such patients is still debatable—especially given that the evidence in favour of administering chemotherapy derives from a few small trials[10,11]. Nevertheless, many oncologists believe that chemotherapy is appropriate for patients who are not as fit as the ones enrolled in clinical trials[12]. Elderly patients are also frequently underrepresented in clinical trials, and treatment might therefore be withheld from them in actual practice[13].

Despite emerging evidence in favour of treating older, "non-fit" patients with advanced lung cancer, clinicians from different specialties often have diverging outlooks on the risks and benefits of cancer therapeutics[14]. Research has shown that oncologists and surgeons have discordant concepts of evidence-based recommendations for the administration of chemotherapy in breast and colorectal cancer[15,16]. Moreover, the studied practitioners mostly disagreed about the optimal treatment for older patients with a relatively poor PS[16].

Data from various regional cancer care centres in Ontario showed that a significant proportion of patients (20%–48%) with inoperable stage III non-small-cell lung cancer (NSCLC) had received no treatment for their disease 6 months after the diagnosis was made[17]. Although referral to a medical oncologist seems to be closely related to the administration of chemotherapy, studies from other Canadian tertiary care centres outlined relatively modest referrals to medical oncologists for patients with resectable NSCLC[18–20].

To better understand the impact of various factors influencing treatment decisions in modern-day practice, we analyzed the characteristics of a recent lung cancer cohort managed at a large university hospital in Quebec. In that retrospective analysis, multiple items were taken into consideration with respect to their direct implications for treatment decisions and survival. Our data could serve as a basis for future studies inquiring into novel therapeutic approaches for certain subgroups of patients believed to be unfit for contemporary treatments. Additionally, our analysis could allow for the identification of strategies that might potentially improve the management of patients with advanced lung cancer.

METHODS

Setting and Study Population

The study was conducted at the Centre hospitalier de l'Université de Montréal (CHUM), one of two major health care networks in the city of Montreal, Quebec. The centre is also a university hospital affiliated with the Université de Montréal. Data available from CHUM's medical archives was used to identify all patients diagnosed with lung cancer between 1 January 2011 and 31 December 2013. Disease stage was determined using the 7th edition of the American Joint Commission on Cancer's staging system[21].

We retrospectively reviewed the clinical records of patients with advanced lung cancer not amenable to surgical resection. Only patients who were treated and followed at CHUM were included in the analysis. Patients diagnosed at CHUM and treated elsewhere were excluded. Patients with stages I and II NSCLC, as well as patients who underwent surgery for stage IIIA disease, were excluded from the analysis. Patients for whom more than 3 variables were missing were also excluded from the analysis.

This study was approved by the CHUM institutional review board.

Analytical Variables

Thoracic oncology fellows reviewed the clinical records for the identified patients from the time of diagnosis until the first notation of death or the date of last contact.

We retained information relating to age at diagnosis, sex, histology, stage, comorbidities, tobacco consumption, central nervous system (CNS) metastasis at diagnosis, and therapeutic approach. Performance status was measured according to the ECOG classification, which ranges from grade 0 (fully active) to grade 5 (dead).

Information relating to treatment consisted of determining whether the patient received therapy. The various lines of therapy administered were subsequently documented. In the present work, "therapy" refers to the use of chemotherapy or tyrosine kinase inhibitors.

The reasons for not treating patients in the first- and second-line settings were also recorded and tabulated using these categories: patient refusal, poor PS, rapidly deteriorating PS or death, and comorbidities. For patients who refused or were deemed too ill to receive therapy, we recorded further information about the consultations received before treatment selection.

Laboratory findings at diagnosis included hemoglobin and creatinine levels.

Statistical Methods

The IBM SPSS Statistics software application (version 21.0: IBM, Armonk, NY, U.S.A.) was used for the statistical analysis. Descriptive statistics are used to present the patterns of treatment delivery. The multivariate analysis used binary logistic regression ("Method Enter"). Survival time was calculated in months and defined as the time from study entry until death or loss of follow up. Survival curves were plotted using the Kaplan–Meier method, and the log-rank test was applied. Survival analysis used the Cox proportional hazards model, and hazard ratios (HRs) were calculated. All statistical tests were conducted at the 5% level, with 95% confidence intervals (CIs).

RESULTS

Characteristics of the Study Cohort

Table I describes the characteristics of the study patients. In total, 715 eligible patients treated at CHUM during the designated period fulfilled the inclusion criteria, and 683 were included in the final analysis after rigorous assessment for missing variables. Median age at diagnosis was 66 years.

Men constituted 52.3% of the study population. Median ECOG PS was 2. The most frequent histology was adenocarcinoma (46.3%), followed by squamous cell carcinoma (14.5%) and small-cell carcinoma (13.9%). A small proportion of patients (12.6%) had no histologic confirmation of pulmonary malignancy. Those patients did not receive treatment because of their poor PS (76.7%) or because they refused further therapeutic or diagnostic interventions. We found that 6.4% of patients had a sensitizing *EGFR* mutation, and 1.2% had an *ALK* gene rearrangement.

Most patients were stage IV at diagnosis (73.5%), and almost two thirds had no brain metastasis at presentation (65.6%). The rate of tobacco consumption in the study population was significant. The goal of therapy was palliative in most cases (86.4%), and a little more than half the patients with NSCLC (52.9%) received no treatment for their cancer. In contrast, 64.2% of patients with small-cell lung cancer (SCLC) received therapy.

TABLE I Patient characteristics

Characteristic	Value	
	(*n*)	(%)
Age group		
<45 Years	10	1.5
45–54 Years	84	12.3
55–64 Years	218	31.9
65–74 Years	209	30.6
≥75 Years	162	23.7
Sex		
Women	326	47.7
Men	357	52.3
Histology		
Adenocarcinoma	316	46.3
Squamous cell carcinoma	99	14.5
Poorly differentiated	85	12.4
Small-cell lung cancer	95	13.9
Other	2	0.3
No histology	86	12.6
TNM stage		
IIIA	104	15.2
IIIB	77	11.3
IV	502	73.5
EGFR mutation (*n*=218 tested)	14	6.4
ALK rearrangement (*n*=169 tested)	2	1.2
Cerebral metastasis at diagnosis		
Absent	448	65.6
Present	157	23
Undetermined	77	11.3
ECOG PS at diagnosis		
0	94	13.8
1	217	31.8
2	171	25
3	161	23.6
4	40	5.9
Tobacco consumption		
Never-smokers	54	7.9
<30 Pack–years	195	28.6
>30 Pack–years	434	63.5

ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Description of the Therapeutic Approach

A little more than half the study cohort (50.5%) received no treatment for lung cancer, and most received only one line of therapy. First-line therapy consisted mostly of platinum doublets (94.4%). Mean time from diagnosis to treatment administration was 2.28 ± 1.14 months.

Of the patients with stage III disease, 68.5% (n = 124) received therapy, and most (86.3%, n = 107) were treated with curative intent.

The decision not to treat patients was, in most cases, attributed to poor PS (43.2%). Patients with a rapidly declining PS or cancer-related complications leading to death (31.9%) did not benefit from cancer-directed therapy either. Patient refusal of therapy (20.9%) and significant comorbidities (4%) were also listed as causes for not administering therapy. We found low rates of referral to medical oncology (32.2%) in patients who did not receive treatment; see Figure 1 for an illustration of the therapeutic approach.

Declining PS was the main reason for no treatment being administered in the second-line setting (79% of patients). Patient refusal (8%), patient death (8%), and associated comorbidities (5%) also affected the choice to refrain from therapy in this setting.

Multivariate analysis assessed the effect of covariates on treatment administration: age, sex, histology, TNM stage, ECOG PS, CNS metastasis at diagnosis, hemoglobin at diagnosis, and creatinine at diagnosis. The analysis (Table II and Figure 2) revealed a statistically significant correlation of treatment administration with these variables: ECOG PS of 0–1 versus ECOG PS of 2 [odds ratio (OR): 7.88], age less than 75 years (OR: 3.68), absence of cerebral metastasis at diagnosis (OR: 2.60), NSCLC histology (OR: 2.38).

Survival Analysis

When treatment was administered to patients with SCLC, a 9-month improvement in the median overall survival (OS) was observed (9.6 months vs. 0.6 months; HR: 0.20; 95% CI: 0.09 to 0.44; $p < 0.001$). Patients with NSCLC who received treatment experienced a median OS improvement of 11.6 months (13.9 months vs. 2.3 months; HR: 0.28; 95% CI: 0.21 to 0.36; $p < 0.001$). An OS benefit was also identified when treatment was given in patients with an ECOG PS greater than 1 (8.2 months vs. 3 months; HR: 0.25; 95% CI: 0.16 to 0.38) and in those more than 75 years of age (13.2 months vs. 3.1 months; HR: 0.44; 95% CI: 0.23 to 0.87), both $p < 0.001$ (Table III, Figure 3).

DISCUSSION

A particularly concerning observation from our analysis involves the high proportion of patients not receiving therapy for their malignancy. Even more disconcerting is the fact that only one third of patients were referred to an oncologist before abstaining from cancer-directed therapies. Comparable rates of therapeutic refrain and low

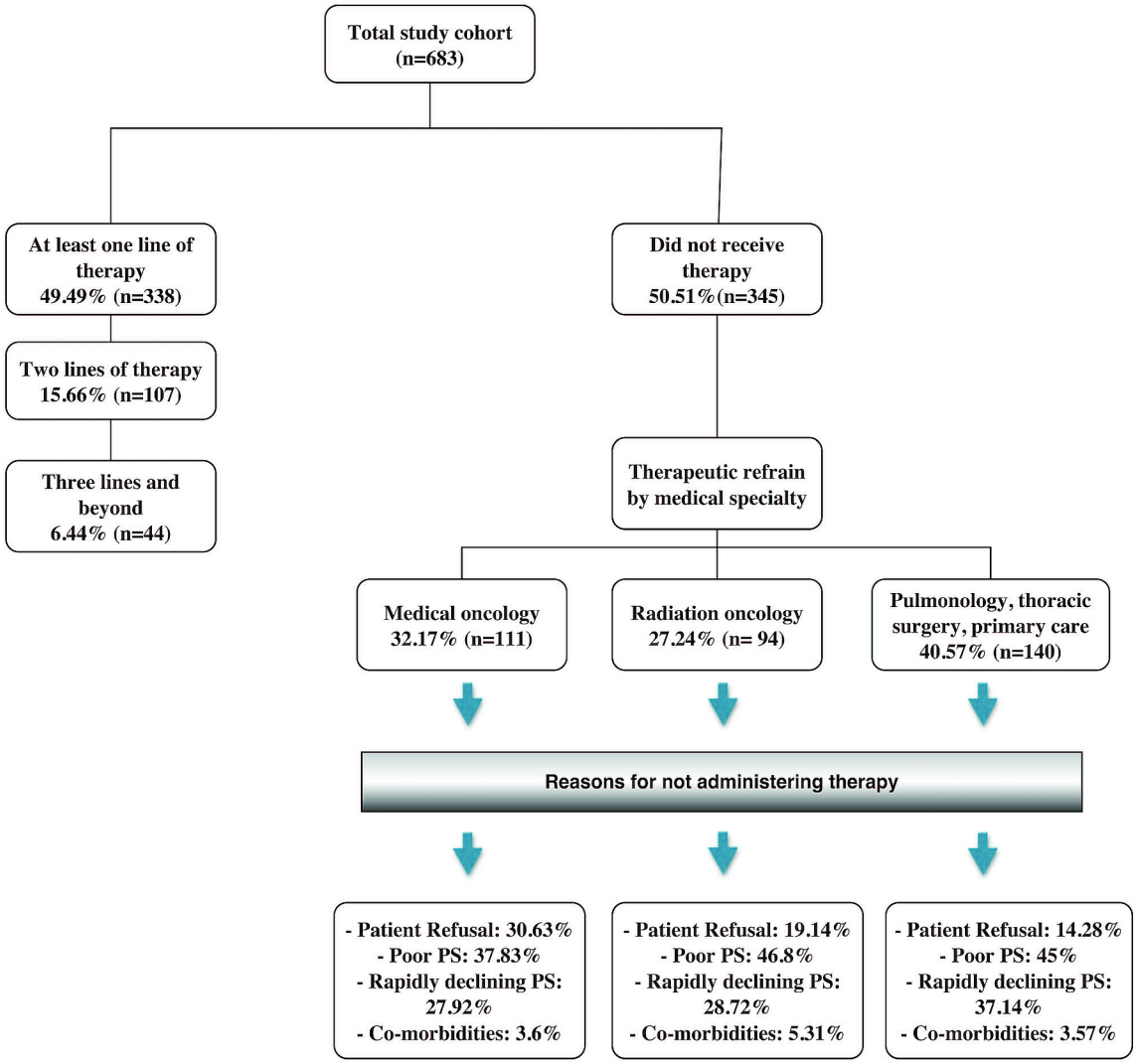

FIGURE 1 The therapeutic approach observed in the study population. Comorbidities consisted of chronic obstructive pulmonary disease (47%), cardiovascular diseases (35%), severe cognitive impairment (8%), chronic kidney disease (6%), and liver disease (4%). PS = Eastern Cooperative Oncology Group performance status.

referral to oncologists were previously described in various regions of Canada in the context of colorectal, breast, and lung cancer[15,18–20]. Two other studies also reported low proportions of treatment use in Canadian patients with advanced lung cancer[17,22]. As in our study, older age and poor PS we also associated with a lower likelihood of receiving therapy[17,22].

In our cohort, advanced age and poor PS were the other variables having a major association with treatment administration. However, patients with a poor PS experienced a substantial improvement in terms of OS when treatment was given. Patients more than 75 years of age also experienced a significant survival benefit with treatment. Those observations, which are comparable to observations reported by several other authors, go against the prevailing belief that age and reduced functional capacity should be categorical components against the selection of treatment for those patients[10,11,14]. Although PS was shown to be the "gold standard" prognostic measure, also evidenced in the present study, that standing does not support the notion that treatment should explicitly be withheld in patients with a poor PS[23,24]. In fact, PS is an entirely subjective evaluation, prone to considerable discrepancies, with clear inter-observer variabilities[25,26]. As such, PS could be overestimated, consequently leading to inappropriate treatment decisions and even lack of referral to an oncologist. One phase III study has already demonstrated a survival benefit with the administration of platinum doublets in patients 70–89 years of age, despite increased toxicity, thus prompting reconsideration of the treatment paradigms in elderly patients with lung cancer[27]. Notably, approximately one third of patients in the latter trial had a PS of 2 and still capitalized on the survival benefit from treatment. Nevertheless, dedicated studies are still needed to better define the role of therapy in such patients. Currently, checkpoint inhibitors have shown considerable efficacy in patients

TABLE II Multivariate analysis assessing factors associated with receipt of chemotherapy in all referred patients with histologically confirmed lung cancer[a]

Variable	Chemotherapy (%)		OR	95% CI	*p* Value
	No	Yes			
ECOG PS					
0–1	16.3	83.9	7.88	4.8 to 12.9	<0.001
2	63.7	36.3	Reference		
Age					
<75 Years	42.2	57.8	3.68	2.02 to 6.71	<0.001
≥75 Years	77.2	22.8	Reference		
CNS disease at diagnosis					
Absent	40.8	59.2	2.6	1.54 to 4.40	<0.001
Present	60.9	31.1	Reference		
Histology					
NSCLC	52.9	47.1	2.38	0.10 to 0.54	0.001
SCLC	35.8	64.2	Reference		

[a] Younger age, good performance status, an absence of CNS metastasis at diagnosis, and SCLC histology predicted for chemotherapy delivery.
OR = odds ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; CNS = central nervous system; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer.

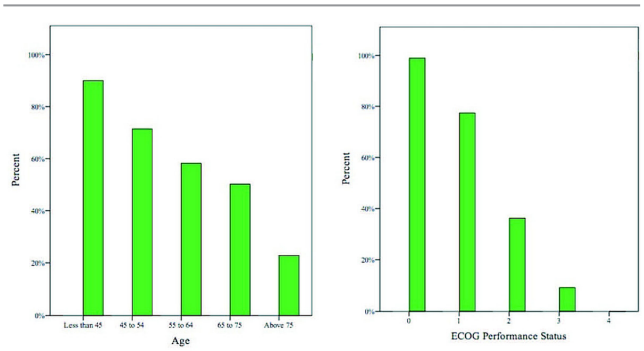

FIGURE 2 Patients who received chemotherapy by (left panel) age and (right panel) Eastern Cooperative Oncology Group (ECOG) performance status.

with NSCLC, but whether those novel agents will play a major role in the treatment of older, "unfit" patients remains unclear[28]. Nonetheless, their toxicity profile is likely to encourage their use in this patient population. The durable responses observed would probably appeal to patients who decline conventional cytotoxic therapy.

Considering the significant correlation of CNS metastasis at diagnosis with poor PS, it seems reasonable that patients with CNS disease at diagnosis would be less likely to receive therapy. The survival of patients with CNS disease has historically been regarded as very poor, and approximately 7%–10% of NSCLC patients present with brain metastases at the time of initial diagnosis[29]. Our data indicate a higher incidence of brain metastasis at diagnosis, possibly because of improvements in imaging techniques in recent years.

Small-cell lung cancer histology was also found to be a predictor of treatment delivery, but that finding is hardly surprising when that cancer's rapid response to therapy is taken into consideration[30].

Existing data describe referral rates to oncologists in the adjuvant setting, but few available data describe referral rates for patients with advanced-stage lung cancer in Canada[22]. In most contexts, low referral is associated with disagreements about the interpretation of current practice guidelines, in which the benefit of administering adjuvant chemotherapy in these particular malignancies was not yet evident for surgeons and primary care physicians[18–20]. However, after careful review of the charts for our study patients, we have come to a "subjective conclusion" that, for nearly all patients who had therapy withheld without referral to an oncologist, management accorded with the evidence-based guidelines and treatment was not denied without valid reason. Nevertheless, early referral to a medical oncologist will serve only to improve patient care, especially given that oncology is an increasingly complex speciality, which translates into lack of awareness on the part of general practitioners with respect to the role of therapy in advanced lung cancer.

Although patient refusal of therapy might be considered a valid reason for not referring the patient to an oncologist, it might be argued that an oncologist could provide cancer patients with a better understanding of the potential value of palliative chemotherapy, thus allowing them to eventually make a "better-informed refusal." Such a refusal should take into consideration improved survival and quality of life weighed against the much-dreaded side effects of treatment, given that most patients are distinctly influenced by what they have witnessed in other cancer patients, which will undoubtedly cloud the notion of cancer treatments[31,32].

In addition to providing insight into the drivers of treatment decisions, our results also provide some context for the current epidemiology of lung cancer in Quebec, which appears to be comparable to that in the reported literature in terms of median age at diagnosis, incidence by sex, and distribution by histologic subtype, with

TABLE III Survival analysis

Variable	Chemotherapy				HR	95% CI	*p* Value
	Yes		No				
	OS	95% CI	OS	95% CI			
Non-small-cell lung cancer	13.9	12.5 to 15.3	2.3	1.8 to 2.8	0.28	0.21 to 0.36	<0.001
ECOG PS = 2	8.2	4.7 to 11.6	3	4.9 to 10.6	0.25	0.16 to 0.38	<0.001
Age ≥ 75 years	13.2	11.1 to 15.2	3.1	2.4 to 3.8	0.44	0.23 to 0.87	<0.001
Small-cell lung cancer	9.6	7.6 to 11.5	0.6	0.1 to 1.1	0.20	0.09 to 0.44	<0.001

OS = overall survival; CI = confidence interval; HR = hazard ratio; ECOG PS = Eastern Cooperative Oncology Group performance status.

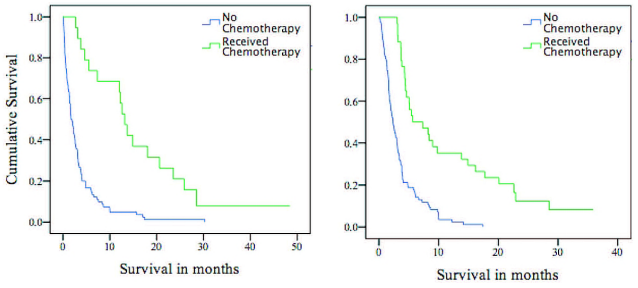

FIGURE 3 Overall survival for chemotherapy-treated and -untreated patients with metastatic non-small-cell lung cancer and (left panel) an Eastern Cooperative Oncology Group performance status of 2, or (right panel) an age of more than 75 years.

adenocarcinoma being the most common histology, followed by squamous cell carcinoma and SCLC[2]. Rates of *EGFR* mutation and *ALK* gene rearrangement were less than those reported in other white populations, but our results are congruent with descriptive data from a recent Canadian cohort[33–35].

Since the publication of the U.S. Surgeon General's report on smoking and health in 1964, the yearly consumption of cigarettes has drastically declined in Canada[36]. However, with 14.6% of Canadians still actively smoking, the associated public health implications are likely to be observed over the next few decades, as demonstrated by our cohort, most of whom had considerable tobacco exposure. Although all histologic lung cancer subtypes were related to tobacco consumption, we detected a higher prevalence of squamous cell carcinoma and SCLC in patients with more intense tobacco exposure, which is consistent with previously published epidemiologic studies[37].

Finally, time from diagnosis to treatment, despite its apparent length in our cohort, is quite comparable to that in reports from other Western countries, where wait times ranged from 54 days to 120 days[38,39]. Still, approximately one third of our patients received no treatment because of a rapidly deteriorating PS, which should be interpreted as an unmet need in our health care system. Shortening the diagnostic and treatment delay times might be a difficult task, but it is one that should be attempted by prioritizing access to diagnostic procedures for patients with a presumptive diagnosis of lung cancer. A study similar to ours was recently conducted in Ottawa, and it also reported low rates of treatment administration in patients with advanced NSCLC (45% of patients did not receive treatment)[40]. Brule *et al.*[40] refer to a Cancer Assessment Clinic, together with implementation of the Lung Transformation Project, that provides expedited diagnostic procedures and early referral to oncologists and seems to have reduced wait times by approximately 40% during its first 6 months of operation[40]. Similar programs could be adopted in other provinces, potentially increasing access to therapeutic interventions. Other worthy undertakings in this context involve raising patient awareness and advocating for lung cancer screening programs in high-risk individuals, especially given that the National Lung Cancer Screening Trial demonstrated a survival benefit in favour of screening[41]. Although the ultimate goal of screening programs would be to unmask early-stage disease, patients with asymptomatic advanced disease could also be diagnosed earlier, which would eventually lead to earlier referral for therapeutic management while the patient still has a good PS.

Despite some limitations, mainly because of its retrospective nature, our study provides a real-world description of patients with advanced lung cancer, including a comprehensive assessment of patient demographics and survival. Furthermore, the study is the first of its kind in the Quebec region, and it raises several key questions relating to lung cancer management. Most importantly, the proportion of patients not receiving therapy warrants further scrutiny in the hopes of identifying potential interventions that might lead to early referral to specialized care. Another consequential issue concerns the treatment of older and sicker patients, particularly in the context of an aging population.

CONCLUSIONS

Our analysis highlights a relatively low rate of treatment administration for patients with advanced lung cancer. Older patients and those with a relatively poor PS were more likely to be referred to supportive care rather than to receive life-prolonging and disease-targeted treatments. The status quo cannot change as long as half those patients do not receive therapy. Effective strategies that might lead to treatment administration include nationwide policies that would prioritize diagnostic procedures for patients with suspected lung cancer, thereby reducing stage migration and cancer-related complications that ultimately lead to a rapid decline in PS and subsequent refrain from therapy. Additionally, the identification of novel molecular

diagnostic procedures such as circulating tumour DNA would also reduce delays related to obtaining adequate biopsy specimens. Finally, newly emerging immunotherapy-based regimens could be a foreseeable option for frail elderly patients and those with a relatively poor PS.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: EK reports personal fees from Lilly, Sanofi Canada, Amgen, Celgene, and Bristol–Myers Squibb outside the submitted work. MF reports personal fees from Lilly, Merck, and Boehringer Ingelheim outside the submitted work. MT reports personal fees from Lilly, Amgen, and Celgene outside the submitted work. NB reports personal fees from Merck, Pfizer, AstraZeneca, and Bristol–Myers Squibb outside the submitted work. ST has no conflicts to declare.

AUTHOR AFFILIATIONS

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