Treatment Delays in Non-small Cell Lung Cancer and Their Prognostic Implications

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Introduction: The impact of treatment delays on survival of patients with non-small cell lung cancer (NSCLC) is uncertain. Although later treatment could negatively affect psychological well-being, the maximum acceptable waiting time has not been determined.

Methods: We analyzed consecutive patients with NSCLC between January 2005 and May 2007 in our center. Treatment delay was calculated from the first abnormal radiographic study. Cox proportional hazards analysis was used to identify predictive factors and log-rank tests to compare survival.

Results: Four hundred ninety-five cases were identified; shorter treatment delays were associated with a poor prognosis. Conversely, for every week that the treatment could be delayed, the hazard ratio was improved at 0.97 ($p = 0.05$). Standard treatment was given to 319 of these patients who were separated in localized, regional, and advanced stages. The median treatment delay was 73 days and distributed as follows: 85, 94, and 50 days for localized, regional, and advanced stages, respectively ($p < 0.01$). For localized or regional stages, the association between treatment delay and survival was inconclusive. In the advanced group, each week of treatment delay had a hazard ratio of 0.93 ($p = 0.009$). Survival of advanced patients who began treatment earlier versus later than the group median was 6.8 versus 11.6 months ($p = 0.027$).

Conclusions: For patients with advanced NSCLC receiving equivalent chemotherapy regimens, shorter treatment delays were associated with shorter survival. We hypothesize that urgent treatment carried a negative prognostic meaning, as this was preferentially offered to patients presenting with a higher symptom burden, which conferred them a worse outcome.

Key Words: Non-small cell, Treatment delays, Survival, Standard treatment.

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Lung cancer is the leading cause of cancer-related death throughout the world affecting especially industrialized countries.[1] Most patients present with advanced-stage disease for which the treatment remains palliative.[2] Quebec is one of Canada's most affected provinces, with mortality rates similar to those of the five next common cancers combined (colon, breast, pancreas, prostate, and lymphoma).[3]

The diagnostic workup is often a lengthy process, involving a complex algorithm and serial procedures (bronchial or percutaneous biopsy, mediastinal lymph node sampling, and evaluation for distant metastases), as described in the American College of Chest Physicians 2nd edition guidelines.[4] Canada's healthcare system is publicly funded and can occasionally become encumbered by a rising patient burden.[5] These required sequential investigations in non-small cell lung cancer (NSCLC) generate concerns for increased waiting time to access consultative, diagnostic, and treatment services.

A number of prognostic factors have been described in NSCLC. The most reproducible ones include stage of disease, performance status (PS), and weight loss[6,7]; there is considerable interest lately in molecular biomarkers such as epidermal growth factor receptor and k-ras mutations, among others.[8,9] It is still uncertain whether increases in the treatment delays are associated with stage progression or otherwise compromised patient outcome. This study is a retrospective analysis of patients with NSCLC treated at our institution evaluating several prognostic factors, including treatment delays.

PATIENTS AND METHODS

Hôpital du Sacré-Coeur de Montréal, Canada, is a 600 in-bed teaching hospital, serving the northern Montreal metropolitan area. Thoracic surgery and chemotherapy are available on site, and positron emission tomography, transesophageal biopsy, and radiotherapy are available off site on a priority consultation service.

Patients with a histological diagnosis of NSCLC in our center between January 2005 and May 2007 were entered into this study. Data were collected from our local tumor registry, a retrospective database built following the standards set forth by the American College of Surgeons. New cases of NSCLC were identified as follows: a computer search of hospital discharge diagnoses was run through the hospital's electronic database; in addition, a comprehensive manual search of all pathology reports and outpatient pulmonology and oncology

clinics was performed. Information was also complemented from the radiology database and from patient chart review. Staging was done using the sixth tumor, node, metastasis (TNM) classification,[10] and pathological staging, when available, was prioritized over clinical staging. Treatment delays were calculated from the date of the first abnormal radiology study that was suspicious for lung cancer, and survival was calculated from the start of treatment. The institutional research ethics board approved this study.

Statistical analyses were done using the SPSS 17.0 software. Simple statistics included the χ^2 test to compare proportions and the Mann-Whitney *U* test to compare treatment delays as they displayed a non-normal distribution curve. Survival curves were generated using the Kaplan-Meier method, and the log-rank test was used for comparison. Both univariate and multivariate Cox regression models were used to explore the association between survival and different patient characteristics.

Patients received a wide array of treatments, according to their disease stage, comorbidities, and/or PS. The treatment approaches were categorized as standard, if they were considered to be appropriate for the patient's stage: surgery for stages I and II +/− adjuvant chemotherapy, multimodality treatment for stage III, and platinum-based chemotherapy for stage IV. Alternative antineoplastic treatments, given to patients with altered PS or limited cardio-respiratory function, were categorized as nonstandard (i.e., radiotherapy for localized disease, single modality treatment for regional disease, or antineoplastic treatment other than platinum-based chemotherapy for advanced disease); finally, hospice care consisted of symptom management alone.

RESULTS

Diagnostic Cohort

Six hundred sixty-five patients received a diagnosis of primary lung cancer during the study period. In 56 of them, no histopathology was available, 3 patients were diagnosed with carcinoid cancer, and 1 had sarcomatoid carcinoma. In the remaining 605 patients, 89 (15%) had small-cell histology and 516 (85%) had NSCLC. Most patients presented with advanced stages at diagnosis, as 60% were III-B or IV.

Out of this diagnostic cohort, 21 patients did not return for medical care to our hospital and the remaining 495 patients were retained for outcome analyses. The types of treatment received were categorized as follows: standard treatment for 319 (64%) patients, nonstandard treatment for 92 (19%) patients, and hospice care for 84 (17%) patients.

When analyzed by disease stage, a lower proportion of patients could receive a standard treatment as stage increased; 84% of stages I and II, 67% of stage III, and 46% of stage IV patients (Figure 1).

Treatment delay data were available in 85% of patients referred for hospice care (time from abnormal image to hospice care decision), 98% of patients receiving a nonstandard treatment, and 100% of patients receiving a standard treatment. The median treatment delay of the whole group was 62 days (25–75% interquartile range [IQR] = 30–108 days). The shortest delays were for hospice care (29 days) and the longest were for starting a standard treatment (73 days), $p < 0.022$ (Table 1).

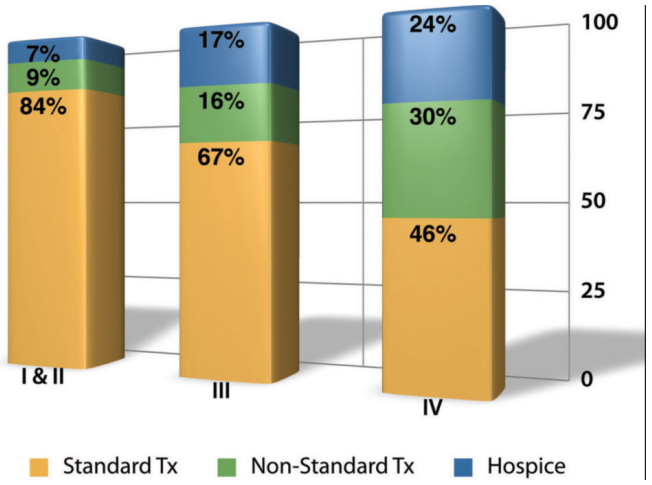


FIGURE 1. Distribution of treatment groups according to disease stages ($n = 495$). Standard indicates recommended treatments for the respective disease stage; nonstandard indicates alternative antineoplastic treatments; and hospice indicates symptom management alone.

Several factors were analyzed in a Cox proportional hazards model for survival ($n = 495$ patients): age, gender, smoking history, histology (squamous versus other), type of treatment (hospice versus nonstandard versus standard), disease stage, and treatment delays. These variables were selected as generally recognized to have prognostic value[6,7] or interesting to study (treatment delays). Other factors were not entered in the analysis because of lack of sufficient data: race, weight loss, PS, and oncogenic mutations. Type of treatment, disease stage, and treatment delays were significantly associated with overall survival, both in uni- and multivariate analyses (Table 2). Nonstandard treatment and hospice care were poor and very poor prognostic factors, respectively, compared with standard treatment. Advanced stage of disease was also confirmed as a poor prognostic factor. Finally, treatment delays were significantly associated with survival ($p = 0.005$); for every week that the treatment could be delayed, the multivariate hazard ratio (HR) was 0.97 (95% confidence interval [CI] = 0.96–0.99). For every month of treatment delay, survival was proportionally improved with a HR of 0.89 (95% CI = 0.82–0.97). We sought to analyze this association in more detail within the standard treatment group.

TABLE 1. Treatment Delays According to Treatment Group

Approach	Median (d)	25–75% IQR
Hospice care ($n = 71$)	29	16–57
Nonstandard treatment ($n = 90$)	51	21–110
Standard treatment ($n = 319$)	73	42–110
All ($n = 480$)	62	30–108

IQR, interquartile range; *n*, patients with available data.

TABLE 2. Uni- and Multivariate Analyses for Survival for the three Treatment Cohorts ($n = 495$)

	Univariate		Multivariate	
Variables	***p***	**HR**	***p***	**HR**
Types of treatment	<0.001		<0.001	
Standard		Reference		Reference
Nonstandard		2.04		1.60
Hospice care		5.56		7.26
Stages	<0.001		0.001	
I and II		Reference		Reference
III		2.33		2.14
IV		5.65		5.87
Treatment delays	<0.001		0.005	
1 wk		0.95		0.97
1 mo		0.81		0.89

Other factors used in the analysis were age, gender, smoking history, and histology.
HR, hazard ratio.

Standard Treatment Cohort

The characteristics of the 319 patients who received a standard treatment are listed in Table 3. They were separated into three groups according to their TNM staging and the intended treatment: localized ($n = 127$), regional ($n = 68$), and advanced ($n = 124$). Their treatments are described in the following section.

Patients with localized disease included stages I and II and were treated with surgery. Lobectomy was the most common procedure ($n = 103$), followed by sublobar resection ($n = 18$) and pneumonectomy ($n = 6$). Among the patients with stages IB and II, 20% received adjuvant chemotherapy.

The cohort with regional disease included most of stage III (36 and 32 patients in stages IIIA and IIIB, respectively) and was treated with a combined approach. Surgery was performed in 31 patients, and 50% received either pre- or postoperative chemotherapy. In the remaining 37 patients, a chemoradiation approach was used, either concomitantly in 75% or sequentially in 25% of them. Twelve percent of the regional group patients were presented at multidisciplinary tumor board discussions.

The cohort with advanced disease included patients with stages IIIB ($n = 26$) not eligible for radical radiotherapy and stage IV ($n = 98$). Out of the stage IV patients, 27% had brain metastasis at diagnosis. Chemotherapy consisted of a platinum-based doublet; carboplatin was used in 114 (92%) regimens, combined with gemcitabine ($n = 95$), vinorelbine ($n = 11$), taxol ($n = 7$), or etoposide ($n = 1$), and cisplatin + vinorelbine was given to the remaining 10 (8%) patients. Forty percent of patients received radiotherapy before starting chemotherapy. The median number of chemotherapy cycles was 4 (range 1–6). Thirteen percent of patients were enrolled in research protocols with investigational agents, and they were analyzed within this group.

Second-line chemotherapy was administered to 57 (47%) patients in the advanced group and to 13 patients who relapsed from the local and regional groups after their primary treatment. The most frequently used second-line regimen was taxotere in 60% of cases, followed by tyrosine kinase inhibitors and pemetrexed. Out of the 70 patients receiving second-line, 35 (50%) received a third-line treatment. The most frequently used drug in the third-line treatment was erlotinib in 60% of cases, followed by taxotere and pemetrexed. Fourth-line treatment was subsequently given to eight of these patients.

We compared the treatment delays for the three groups of patients: localized, regional, and advanced (Table 4). This represented time from abnormal radiology to either surgery—for localized, multimodality—for regional, and chemotherapy—for advanced patients. The advanced group had the shortest treatment delay of 50 days when compared with the localized and regional groups who had a median treatment delay of around 3 months ($p < 0.001$).

TABLE 3. Characteristics of Patients Receiving Standard Treatment

Characteristics	***n* = 319**
Age (yr), median (range)	62 (26–82)
Gender	
Men	55%
Women	45%
Histology	
Squamous	23%
Other NSCLC	77%
Smoking	
Yes	88%
No	3%
Unknown	9%
Pack-years, median (range)	42 (5–125)

NSCLC, non-small cell lung cancer.

Outcomes of the Standard Treatment Cohort

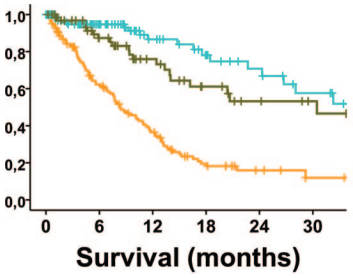
With a median follow-up of 8 months, 193 (61%) of the patients were still alive. Overall survival separated by the three-stage groups is shown in Figure 2. Median survival times estimated by the Kaplan-Meier method were 35 months for localized, 30 months for regional, and 8 months for the advanced group ($p < 0.001$).

Several factors were analyzed for their prognostic association with survival. Given the fact that there were relatively few events (deaths) within the localized and regional groups (19 and 20 deaths, respectively), they were combined together for the proportional hazards analysis. There were 87 deaths in the advanced group, which was analyzed separately.

TABLE 4. Treatment Delays According to Disease Extent ($n = 319$)

Stages	**Median (d)**	**25–75% IQR**
Localized ($n = 127$)	85	58–130
Regional ($n = 68$)	94	60–121
Advanced ($n = 124$)	50	30–76

IQR, interquartile range.



Stage	Median (mo)
Localized	35
Regional	30
Advanced	8

FIGURE 2. Survival of 319 patients receiving standard treatment according to stage.

Common factors, used in all the analyses, were age, gender, smoking status, histology, and treatment delays, which were considered as a continuous variable. Factors specific for the local-regional group were disease stage (local versus regional and pathological versus clinical) and tumor board presentation. Factors specific for the advanced group were disease stage (IIIB versus IV), prior radiation therapy, brain metastasis, and research protocol enrolment.

For the local-regional group ($n = 195$), the only significant factor associated with survival was age; in univariate analysis, the HR was 1.05 (95% CI = 1.01–1.09, $p = 0.015$). In the multivariate analysis, the HR was 1.06 (95% CI = 1.01–1.10, $p = 0.01$). None of the other factors analyzed, including treatment delays, were associated with survival.

For the advanced group ($n = 124$), the only significant factor associated with survival was treatment delay. The univariate HR was 0.94 (95% CI = 0.91–0.98) for every week that the treatment could be delayed and 0.78 (95% CI = 0.65–0.93) for every month of delay ($p = 0.006$). In multivariate analyses, for every week of delay, the HR for survival was 0.93 (0.88–0.98). Proportionally, every month of treatment delay was associated with an improved survival by a HR of 0.74 (0.59–0.93), $p = 0.009$. Figure 3 shows overall survival of advanced patients according to the treatment delay compared with the median wait time, which was 50 days. The median survival of patients who were treated on a more urgent basis (wait time lower than median) was 6.8 months, when compared with 11.6 months for patients with treatment delays beyond the median, $p = 0.027$.

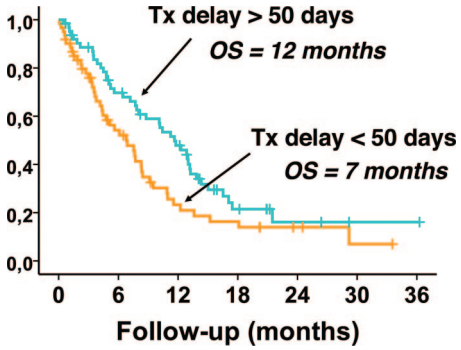


FIGURE 3. Overall survival of patients with advanced disease according to length of delay ($n = 124$). OS, overall survival; Tx, treatment.

DISCUSSION

One of the most important prognostic factors in NSCLC is the TNM stage. Unfortunately, the majority of patients present with an advanced stage at diagnosis, contributing to their relatively limited overall survival. In this analysis, we sought to describe our local experience with the epidemiology and outcome of the disease and look for prognostic factors.

The traditional model of NSCLC natural history has been challenged recently. The theory of local growth and progression toward loco-regional invasion and distant metastasis predicts that an earlier diagnosis and treatment should improve survival. Results from screening studies so far have not convincingly proven this concept and it is possible that asymptomatic nodules discovered through screening have a different natural history and perhaps do not represent precursors of advanced cancer.[11] Furthermore, data from the International Adjuvant Lung Cancer Trial[12] and its recent update[13] show that approximately 60% of patients operated for early-stage disease eventually developed local or distant recurrence, suggesting that micrometastases could occur much earlier than they become clinically apparent in unscreened patients.

Canada's healthcare system faces, among other constraints, an increase in the incidence of patients with cancer. In this context, an analysis of delays in receiving standard treatment and their association with survival in NSCLC becomes interesting, and, to our knowledge, this is one of the first studies in this particular setting.

Treatment delays in our center could be either system related, because of delays in diagnostic or treatment procedures, or patient related, because of their noncompliance, and no distinction could be made between the two. System-related delays between the first abnormal radiology study and treatment initiation were multifactorial (data not shown); they included waiting times for physician appointments (pulmonologist, thoracic surgeon, cardiologist, radiation, and/or medical oncologist), diagnostic tests or procedures (computed tomography, positron emission tomography, bronchoscopy, mediastinoscopy, endoscopic ultrasound, pathological examination, and cardiac and pulmonary function testing), and treatment planning and initiation.

Other studies have found similar trends; a report from Sweden[14] using data from the regional cancer registry reported a median symptom to treatment delay in NSCLC of 4.6 months. Patients with advanced stages of disease had the

shortest treatment delay. In the multivariate analysis, shorter treatment delays were associated with poor survival even after correcting for disease stage, and the highest impact was found within the advanced stages. In another study from Finland,[15] a similar pattern of worse outcome with short treatment delay was seen in advanced stages of disease but not in those with limited disease. The median treatment delay in this study was 112 days, and it was shorter for patients with advanced disease.

Two other studies reported on treatment delays in lung cancer, and their global results (all stages and treatment approaches combined) were the following: one report from France[16] found a median of 62 days starting from the first symptom and another study, from Ireland,[17] reported 54 days from general practitioner referral to treatment. There are several differences with our study, like the probable inclusion of small-cell histology and/or different definitions of the diagnosis date; however, globally, these waiting times seem comparable with those presented in this study. In some of the above-mentioned articles, treatments were grouped into surgical, nonsurgical, and supportive.

In our study, we were able to show that, even when the treatments were categorized according to the recommended approach for the stage, these findings still held for advanced patients. We separated out the patients who were not able to tolerate standard chemotherapy and whose median survival was shorter; the subset of stage IV patients receiving hospice care or nonstandard antineoplastic treatment survived for a median of only 16 and 109 days, respectively. The standard treatment cohort received platinum-based chemotherapy within the same center; in this more homogenous group, the treatment delay was significantly associated with survival in multivariate analysis; for every week that the treatment could be delayed, survival was better by 7%. When the same group was separated according to the median delay, the overall survival was almost double for patients who could initiate treatment later versus those who needed to be treated earlier than 50 days (11.6 versus 6.8 months).

The reasons why the "early" treatment group had a shorter survival are unclear. Adverse prognostic factors present in this group might have been: worse PS, weight loss, comorbidities, and/or molecular biomarkers, which were not available for analysis. Another possibility is that patients having more symptoms came to medical attention and were referred for workup and treatment sooner than those having less or no symptoms. Although these data are not available, the "early" treatment group might have included more symptomatic patients than the "delayed" group, which conferred them a worse prognosis. This would corroborate with reports suggesting that symptom burden is a negative prognostic factor[18] and that their improvement with treatment correlates with better survival.[19]

One of the limitations of this study is its retrospective nature, which lead to some missing data, as mentioned (PS, weight loss, and comorbidities). These variables are not routinely documented in cancer registries according to current standards and have proven difficult to extract from medical charts of unselected patients. Nevertheless, a prospective randomized trial on treatment delay would be clinically and ethically unacceptable. A hospital-based registry could, on the other hand, be modified to prospectively collect information on such variables and facilitate further studies, provided appropriate measures are taken to improve their recording in the medical chart.

We could not find any indication that our waiting times adversely impacted outcome because of disease progression. Waiting times were longer in localized and regional stages than in advanced disease (85, 94, and 50 days, respectively), leaving no indirect evidence of stage progression during the wait time. These differences are probably a reflection of the longer waiting times to adequately diagnose and treat localized and regional disease compared with advanced disease. Indeed, in our experience, it took fewer diagnostic steps to complete the staging and comorbidity evaluations of advanced patients, compared with the loco-regional ones.

In addition, there was no indirect evidence of patients' general status deterioration during the waiting time. Patients referred for hospice care, mostly for decreased PS, had the shortest waiting time followed by patients referred for nonstandard antineoplastic treatments (29 and 51 days, respectively). The longest waiting times were experienced by patients treated with standard approaches (73 days) who also represented the majority of the group (64%).

With regards to localized and regional patients, no conclusive association could be found between treatment delays and overall survival. These findings are similar to those from a study done in the United States,[20] which included patients with stages I to III NSCLC being treated in both public and private hospitals and reported image-to-treatment intervals. Patients in the public system had a significantly longer treatment delay than those from the private hospitals (76 versus 45 days, respectively). Nevertheless, no association could be found between waiting time and survival, despite comprehensive data analysis.

For the local and regional stages, we further analyzed the 3-month treatment delay, with regards to the timing of the pathological diagnosis of NSCLC. In 105 patients, repeated attempts at tissue sampling were nondiagnostic before the therapeutic surgical resection. Their diagnostic and treatment delays were therefore the same, at 88 days (25–75% IQR = 58–130 days). For the remaining 90 patients, pathological diagnosis was successful before definitive treatment, through bronchoscopy, mediastinoscopy, percutaneous, or transesophageal biopsy. Their median delays between radiological and pathological diagnosis were 31 days (25–75% IQR = 13–57 days). Thereafter, their median delays between pathological diagnosis and treatment were 56 (25–75% IQR = 43–70) days for the localized patients (treated by surgery) and 61 (25–75% IQR = 37–88) days for the regional patients (treated by chemoradiotherapy). All these intervals included also delays for physician appointments and imaging studies.

These intervals should be compared with the tumor doubling time in NSCLC, which was estimated to be around 3 months for squamous cell tumors and around 6 months for adenocarcinomas.[21] It is therefore suspected that our median

of approximately 2 months of treatment delay did not significantly impact survival in our cohort.

Finally, treatment delays are very likely to have a negative impact on patients' psychological well-being and indirectly on their quality of life, parameters not available for our analysis. Multidisciplinary tumor board presentations have greatly increased since 2007 in our center. One of the objectives was to speed up the diagnostic and treatment planning process especially for the loco-regional stages and, thereby, decrease the waiting times and patients' anxiety.

In conclusion, our study shows that patients with advanced NSCLC were treated within a shorter delay than those with local and regional stages. For the latter, the relationship between outcome and treatment delay was inconclusive. With equivalent chemotherapy protocols, advanced patients treated on a more urgent basis had a worse survival. We hypothesize that urgent treatment might be a surrogate marker for higher symptom burden, and this parameter would be useful to collect in future prospective studies.

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