

Understanding clinical practice and survival outcomes in patients with unresectable stage III non-small-cell lung cancer in a single centre in Quebec

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ABSTRACT

Methods A retrospective cohort study considered patients 18 or more years of age diagnosed between January 2007 and May 2018 with unresectable stage III non-small-cell lung cancer (NSCLC) who received combined chemoradiation (CRT). Survival was analyzed using the Kaplan–Meier method to determine median overall (OS) and progression-free survival (PFS) and the associated 95% confidence intervals (CIs). Cox regression analysis was performed to identify factors prognostic for survival, including age, sex, smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, treatment type, tumour size, and nodal status.

Results Of 226 patients diagnosed with unresectable stage III disease, 134 (59%) received combined CRT. Mean age was 63 years; most patients were white, were current smokers, had an ECOG PS of 0 or 1, and had nonsquamous histology. Median PFS was 7.03 months (95% CI: 5.6 months to 8.5 months), and OS for the cohort was 18.7 months (95% CI: 12.4 months to 24.8 months). Of those patients, 78% would have been eligible for durvalumab consolidation therapy. Univariate analysis demonstrated a significant OS benefit ($p = 0.010$) for concurrent CRT (cCRT) compared with sequential CRT (sCRT). Disease-specific survival remained significantly better in the cCRT group ($p = 0.004$). No difference in PFS was found between the cCRT and sCRT groups. In addition, tumour size and nodal involvement were significant discriminating factors for survival ($p < 0.05$). In this patient cohort, 64% of patients progressed and received subsequent therapy. Based on multivariate analysis, tumour size and nodal station were the only factors predictive of survival in patients with unresectable stage III NSCLC treated with CRT.

Conclusions Combined CRT has been the standard treatment for unresectable stage III NSCLC. In our study, a trend of better survival was seen for cCRT compared with sCRT. Factors predictive of survival in patients with stage III disease treated with CRT were tumour size and nodal station. Most patients with stage III disease would potentially be eligible for durvalumab maintenance therapy based on the eligibility criteria from the PACIFIC trial. The use and effectiveness of novel treatments will have to be further studied in our real-world patient population and similar populations elsewhere.

Key Words Lung cancer, stage III disease, combined chemoradiation

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INTRODUCTION

In 2020, 8600 Quebecers are expected to be diagnosed with lung cancer. Lung cancer is also expected to be the leading cause of cancer death, accounting for 25.5% of all cancer deaths in Quebec^{1,2}. The 5-year overall survival (OS) of patients with lung cancer varies by stage. Patients diagnosed

at earlier stages of disease experience longer survival than do those diagnosed at more advanced stages, with 5-year OS rates being as high as 73% for patients with stage IA lung cancer and as low as 2% for those with stage IV disease³.

Stage III NSCLC is highly heterogeneous, with disease presentations ranging from resectable tumours with occult microscopic nodal metastases to tumours that are

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non-operable, with a large burden of nodal involvement^{4,5}. The incidence of stage III lung cancer in Canada ranges from 13.5 cases per 100,000 individuals in Alberta to 20.3 cases per 100,000 individuals in New Brunswick⁶. Population-based data collected from 1995 to 2007 in Alberta and Manitoba showed that, of the more than 8000 patients with NSCLC, 26.4% had stage III disease⁷. The prognosis in stage III NSCLC is poor: 5-year OS is 19%–24% for stage IIIA NSCLC and 7%–9% for stage IIIB NSCLC⁸. Similar information is not available for the province of Quebec.

Treatment in this setting has been limited to concurrent chemotherapy and radiation, an approach that has remained unchanged for more than a decade⁹. Despite treatment being curative, 5-year survival remains poor, being limited to 9%–12% of patients treated with combined chemoradiotherapy (CRT)¹⁰.

Recently, based on results in the PACIFIC trial (see NCT02125461 at <https://ClinicalTrials.gov/>), Health Canada approved durvalumab for patients with unresectable stage III NSCLC. The PACIFIC trial demonstrated a statistically significant improvement in progression-free survival (PFS) and OS^{11–13}. However, real-world data about treatment patterns and clinical outcomes for stage III NSCLC in Canada are limited.

The objective of the present study was to describe treatment patterns and survival, and to assess clinical factors affecting survival in patients with unresectable stage III NSCLC treated at a single academic centre in the province of Quebec over the last 12 years. Our study aimed to contextualize the effect of the PACIFIC trial with real-world experience.

METHODS

Study Design

This retrospective cohort study considered patients diagnosed with stage III NSCLC at the Sir Mortimer B. Davis Jewish General Hospital in Montreal, Quebec. Data were extracted from a clinical database that contains clinical, demographic, treatment, and survival information for cases of lung cancer diagnosed between 1998 and 2018. The lung cancer registry was approved by the institutional review board.

The database created in 2001 uses the Access software application (Microsoft Corporation, Redmond, WA, U.S.A.) and contains multiple tables connected by a primary key. Variables captured include demographics, past medical history, diagnostic tests, disease stage, molecular tests, surgery, timelines and treatment plan, chemotherapy, radiation therapy (RT), imaging, and outcomes.

The long-term goals of creating the database are quality assurance and clinical research that contributes information to the fight against lung cancer (for example, to develop better tests and therapies for lung cancer). The short-term goal is to improve the understanding and predict the outcomes of individual treatments by compiling routine clinical information.

As a routine practice, every patient diagnosed with lung cancer is presented to a multidisciplinary tumour board for staging and treatment plan discussion. Each case

is entered into the database in real time by a data manager at the first tumour board presentation. Cases might be re-presented if outcome or treatment changes (or both) occur. Information is updated in the database at each presentation. The final update takes place after the death of the patient and before the patient's chart is archived.

Patients Selection Criteria

Patients were included if they were 18 years of age or older, had a histologically confirmed diagnosis of NSCLC, and were staged clinically or pathologically as stage III according to the 7th edition of the TNM classification. All patients meeting those criteria were included.

To ensure sufficient maturity of survival data and homogeneity of treatment, only patients diagnosed from January 2007 to May 2018 were analyzed for the study. The database was locked for analysis at 31 August 2018.

Statistical Analysis

Summary statistics are used to describe patient demographics, disease-related characteristics, treatment patterns, and occurrence of adverse events. Means with standard deviation are reported for continuous variables, and frequencies and percentages are reported for categorical variables such as

- patient demographics (age, sex, ethnicity or race, smoking status),
- disease-related characteristics [stage at primary diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, size of tumour, nodal involvement, and mutation status],
- treatment patterns [concurrent CRT (cCRT) and sequential CRT (sCRT)].

These outcome variables were defined:

- Overall survival—the time elapsed from the start of RT to the date of death or last follow-up (all patients)
To align with the PACIFIC trial, an exploratory analysis was carried out to determine OS from the end of RT. To determine disease-specific survival, patients who died of causes unrelated to lung cancer were excluded. Overall survival was also calculated for patients who would have been eligible for durvalumab if it had been available at the time. Patients were considered eligible if they had completed CRT, had not progressed within 14 days of the end of therapy, were not receiving steroids at 10 mg or more daily, and had a good PS.
- Progression-free survival—the time elapsed from the start of RT to the date of progression (progression was determined based on radiologic imaging and response as assessed by the treating physician)

Survival was analyzed using the log-rank test and the Kaplan–Meier method to determine median OS and the associated 95% confidence interval. A Cox proportional hazards model was used to identify factors prognostic for survival. The factors included in the multivariate forward conditional model were age, sex, smoking status, ECOG PS,

histology, treatment pattern, tumour size, and nodal status.

Statistical analyses were conducted using the IBM SPSS Statistics software application (version 20; IBM, Armonk, NY, U.S.A.) for Windows (Microsoft Corporation).

RESULTS

Patient Characteristics

From January 2007 until May 2018, 263 patients were diagnosed with stage III NSCLC; 37 (14%) underwent surgery, and 226 (86%) were deemed to have unresectable disease and were included for analysis. Of those 263 patients, 92 (41%) received either definitive radiation, systemic chemotherapy, or best supportive care (Figure 1). The remaining 134 (59%) were treated with combined CRT. Of those 134 patients, 114 (85%) were treated with cCRT, and 20 (15%), with sCRT.

Mean age of the patients was 65 ± 9.8 years; most were white and ex-smokers or current smokers, and they had an ECOG PS of 0 or 1 and nonsquamous histology. The baseline characteristics of patients treated with cCRT and sCRT were different: the former group were significantly younger and showed a slight prevalence of nonsquamous histology and mostly N1 or single-station N2 disease (Table I). A mediastinal staging procedure was performed in 96 patients from that group (72%), and positron-emission tomography imaging for staging was performed in 93 (69%). The tumour was graded in 75% of cases: well differentiated in 23 (17%), moderately differentiated in 18 (13%), poorly differentiated in 54 (40%), and undifferentiated in 6 (4%, Table I).

These chemotherapy regimens were used:

- Cisplatin–etoposide (modified SWOG protocol)¹⁴: intravenous (IV) cisplatin 50 mg/m² on days 1, 8, 29, and 36 with IV etoposide 50 mg/m² on days 1–5 and 29–33. The RT was started on day 2 of cycle 1 of chemotherapy at 1.8 Gy daily 5 days per week for a total of 25 fractions (45 Gy) to the primary and mediastinum, followed by a boost to the primary and involved nodes of 1.8 Gy daily for up to 8 fractions (15 Gy). The total dose of RT was 60–66 Gy in 30–33 fractions. This modified SWOG protocol was used in 43 patients (32.1%) receiving cCRT treatment.
- Induction chemotherapy followed by CRT¹⁵: induction used 2 cycles of carboplatin–gemcitabine in a 21-day regimen [IV carboplatin 5 AUC (area under the curve) given over 30 minutes on day 1, and IV gemcitabine 1000 mg/m² given over 30 minutes on days 1 and 8]. The CRT started after the induction chemotherapy and consisted of IV paclitaxel 50 mg/m² given over 60 minutes on days 1 and 8 and IV gemcitabine 100 mg/m² given over 30 minutes on days 1 and 8 of each 3-week cycle for 2 cycles. The RT was given at a total tumour dose of 60–66 Gy over 6 weeks, starting with day 1 of chemotherapy cycle 3. This regimen is approved as the standard treatment for stage III NSCLC treatment in Quebec. Two cycles of full-dose induction chemotherapy followed by cCRT was used in 50 patients (37.3%).
- Randomized controlled trials with platinum-based chemotherapy and concurrent RT: chemotherapy according to randomized controlled trial protocol was used in 11 patients (8.2%).

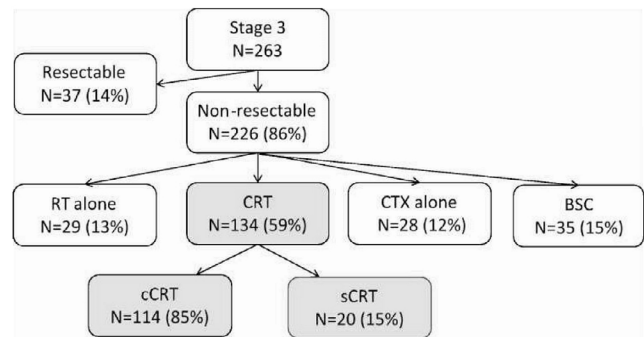


FIGURE 1 Flowchart of patient disposition. RT = radiation therapy; CRT = chemoradiotherapy; CTX = chemotherapy; BSC = best supportive care; cCRT = concurrent chemoradiotherapy; sCRT = sequential chemoradiotherapy.

- Other platinum-based chemotherapy regimens, such as carboplatin–pemetrexed and carboplatin–gemcitabine given with RT with curative intent: one of those chemotherapy regimens with RT was used in 30 patients (22.4%).

Patients Potentially Eligible for Maintenance Durvalumab

After completing initial curative treatment, the 134 patients were followed by their treating pulmonary oncologist every 2–3 months with radiographic imaging. Of those patients, 104 (77.6%) would have been eligible for durvalumab consolidation therapy, and the remaining 30 (22.4%) would have been excluded for these reasons:

- Prematurely stopped radiation therapy (5 patients)
- Progressed within 14 days of ending RT (4 patients)
- Treated with steroids at 10 mg or more daily for treatment complications (15 patients)
- Had a poor ECOG PS (6 patients)

Treatment After Progression

After initial treatment, 86 of the 134 patients (64.2%) had progressed and received subsequent therapy. Most were treated with subsequent chemotherapy (57%). Immunotherapies or targeted therapies were used as treatment in 22 patients (26%, Table II).

PFS and OS

At the time of analysis, mean duration of follow-up was 32 months (range: 2–138 months), with 92 deaths (68.7%) and 86 (64%) progression events having been observed. The PFS was slightly better for patients treated concurrently than for those treated sequentially (Figure 2). Median PFS was 7.97 months for cCRT compared with 5.26 months for sCRT, but the difference was not statistically significant ($p = 0.081$).

Median OS was significantly better for cCRT than for sCRT, whether assessed from the start (Figure 3) or end of RT (Figure 4). The disease-specific survival calculation excluded 14 patients because of death from causes other than lung cancer. The OS in the cCRT group remained significant at $p = 0.004$ (Figure 5).

TABLE I Demographic and clinical characteristics of the patients at diagnosis with stage III non-small-cell lung cancer

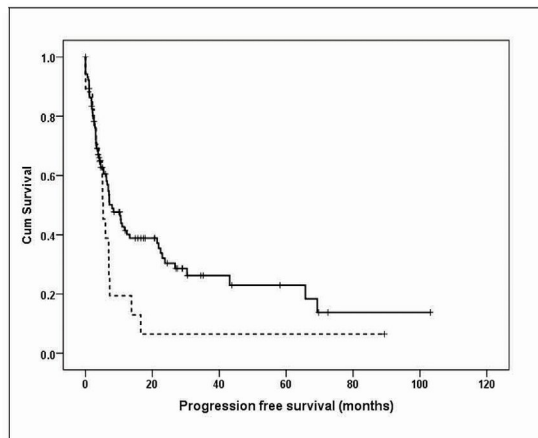
Variable	Stage III unresectable	Stage III treated with CRT			<i>P</i> Value ^a
		Overall	Concurrent	Sequential	
Patients (<i>n</i>)	226	134	114	20	
Age (years)					0.003
Mean	66±10.7	65±9.8	63.4±9.5	70.4±9.2	
Range	31–88	31–82	31–81	50–82	
Sex [<i>n</i> (%)]					0.41
Women	106 (47.0)	67 (50.0)	58 (51.0)	9 (45.0)	
Men	120 (53.0)	67 (50.0)	56 (49.0)	11 (55.0)	
Ethnicity [<i>n</i> (%)]					0.73
White	203 (90.0)	118 (88.1)	99 (86.8)	19 (95.0)	
Asian	16 (7.1)	11 (8.2)	10 (8.8)	1 (5.0)	
Other	7 (2.9)	5 (3.7)	5 (4.4)	0 (0.0)	
Smoking status ^b [<i>n</i> (%)]					0.34
Current smoker	121 (53.5)	70 (52.0)	63 (55.3)	10 (50.0)	
Ex-smoker	80 (35.4)	52 (39.0)	40 (35.1)	9 (45.0)	
Never-smoker	20 (11.1)	12 (9.0)	11 (9.6)	1 (5.0)	
ECOG PS ^b [<i>n</i> (%)]					0.76
0	72 (32.0)	42 (31.3.0)	37 (32.5)	5 (25.0)	
1	140 (61.9)	84 (62.7.0)	70 (61.4)	14 (70.0)	
2	14 (6.1)	8 (6.0)	7 (6.1)	1 (5.0)	
Stage (TNM) [<i>n</i> (%)]					0.17
IIIA	120 (69.0)	99 (73.9)	87 (76.3)	12 (60.0)	
IIIB	106 (31.0)	35 (26.1)	27 (23.7)	8 (40.0)	
Primary tumour size [<i>n</i> (%)]					0.84
≤3 cm	53 (23.6)	46 (34.3)	40 (35.1)	6 (30.0)	
>3 cm and ≤5 cm	83 (36.7)	40 (29.9)	33 (28.9)	7 (35.0)	
>5 cm	90 (39.7)	48 (35.8)	41 (36)	7 (35.0)	
Histology [<i>n</i> (%)]					0.09
Nonsquamous	144 (63.5)	108 (80.6)	93 (81.6)	16 (65.0)	
Squamous	82 (36.5)	26 (19.4)	21 (18.4)	7 (35.0)	
N Stage [<i>n</i> (%)]					<0.001
N1/N2, single station	99 (43.8)	97 (72.4)	97 (85)	0 (0)	
N2, multi-station, or N3	127 (56.2)	37 (27.6)	17 (15)	20 (100.0)	
Mediastinal staging [<i>n</i> (%)]					0.96
EBUS or EUS	62 (27.0)	43 (32.0)	37 (32.0)	6 (30.0)	
TBNA	73 (32.0)	32 (24.0)	27 (24.0)	6 (30.0)	
MED	23 (10.0)	21 (16.0)	17 (15.0)	5 (25.0)	
Not done	68 (30.0)	38 (28.0)	33 (29.0)	3 (15.0)	
Grade [<i>n</i> (%)]					0.78
1	45 (20.0)	21 (16.0)	18 (16.0)	3 (15.0)	
2	29 (13.0)	18 (13.0)	15 (13.0)	3 (15.0)	
3	86 (38.0)	54 (40.0)	50 (44.0)	4 (20.0)	
4	11 (5.0)	6 (4.0)	2 (1.7)	4 (20.0)	
Not done	55 (25.0)	35 (27.0)	29 (25.3)	6 (30.0)	
PET imaging [<i>n</i> (%)]					0.08
Yes	152 (67.0)	93 (69.0)	82 (72)	11 (55.0)	
No	74 (33.0)	41 (31.0)	32 (28)	9 (45.0)	
Subsequent therapy [<i>n</i> (%)]					0.83
Yes	118 (52.2)	86 (64.2)	71 (62.3)	15 (75.0)	
No	108 (47.8)	48 (35.8)	15 (75.0)	5 (25.0)	

^a Comparing concurrent with sequential CRT. Boldface type indicates a significant difference.^b Data missing for 5 patients.

CRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; EBUS = endobronchial ultrasonography; EUS = endoscopic ultrasonography; TBNA = transbronchial needle aspiration; MED = mediastinoscopy; PET = positron-emission tomography.

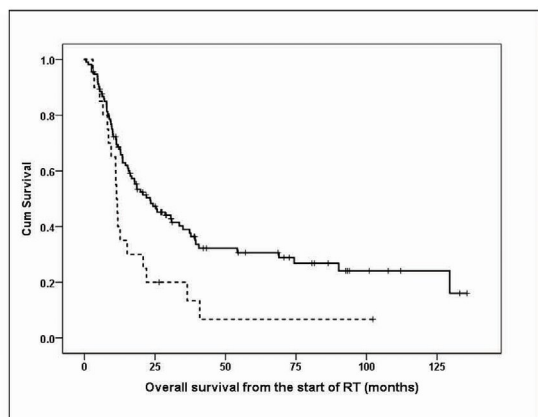
TABLE II Subsequent treatments after first-line treatment

Upon progression from first-line treatment	Patients [n (%)]
Chemotherapy alone	49 (57.0)
Radiotherapy alone (palliative)	15 (17.4)
Immunotherapy	13 (15.1)
Targeted therapy	9 (10.5)



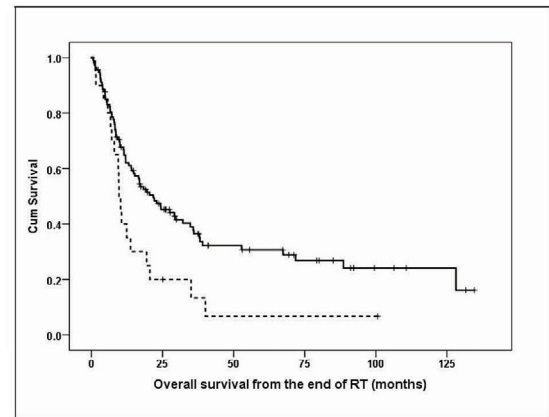
	Median (mo)	95% confidence Interval	
		Lower Bound	Upper Bound
cCRT [—]	7.967	4.749	11.184
sCRT [---]	5.267	4.056	6.477
Overall	7.033	5.565	8.502

Log Rank (Mantel-Cox) = 0.081

FIGURE 2 Progression-free survival by type of combined treatment: concurrent chemoradiotherapy (cCRT) or sequential chemoradiotherapy from the start of radiotherapy (sCRT).

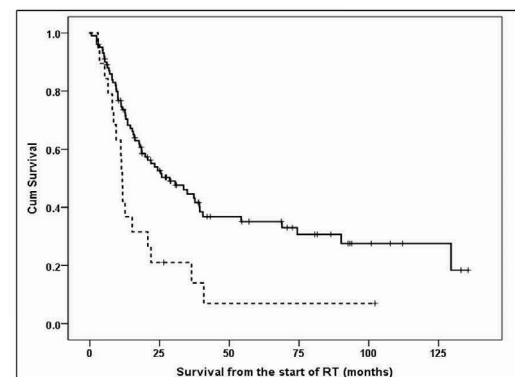
	Median (mo)	95% confidence Interval	
		Lower Bound	Upper Bound
cCRT [—]	23.267	14.295	32.239
sCRT [---]	11.333	10.165	12.502
Overall	18.567	12.357	24.776

Log Rank (Mantel-Cox) = 0.014

FIGURE 3 Overall survival of patients from the start of radiotherapy (RT), by the type of combined treatment: concurrent chemoradiotherapy (cCRT) or sequential chemoradiotherapy from the start of radiotherapy (sCRT).

	Median (mo)	95% confidence Interval	
		Lower Bound	Upper Bound
cCRT [—]	21.733	12.815	30.652
sCRT [---]	9.667	8.206	11.128
Overall	17.100	10.812	23.388

Log Rank (Mantel-Cox) = 0.014

FIGURE 4 Overall survival of patients from the end of radiotherapy (RT), by the type of combined treatment: concurrent chemoradiotherapy (cCRT) or sequential chemoradiotherapy from the start of radiotherapy (sCRT).

	Median (mo)	95% confidence Interval	
		Lower Bound	Upper Bound
cCRT [—]	28.567	15.799	41.334
sCRT [---]	11.633	10.638	12.629
Overall	21.933	13.272	30.595

Log Rank (Mantel-Cox) = 0.004

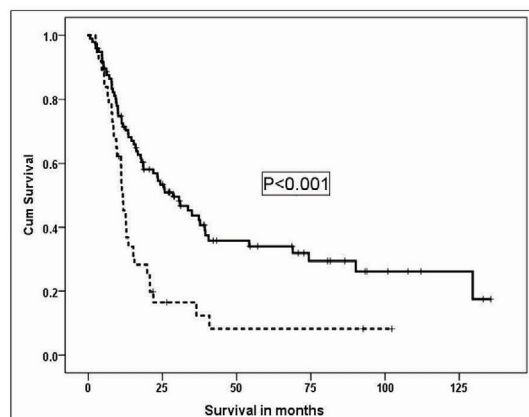
FIGURE 5 Disease-specific survival from the start of radiotherapy (RT), by the type of combined treatment: concurrent chemoradiotherapy (cCRT) or sequential chemoradiotherapy from the start of radiotherapy (sCRT).

Table III shows the results of univariate analyses of survival that included sex, age, smoking status, ECOG PS, histology, type of CRT, size of the tumour, and nodal status. Superior survival was associated with N1 or single-station N2 involvement, a tumour size of 3 cm or less, and being treated with cCRT. Median OS was 28.6 months (95% confidence interval: 18.5 months to 38.6 months) for patients with N1 or single-station N2 involvement (Figure 6). A trend toward survival benefit was observed in patients with nonsquamous histology and female sex.

TABLE III Cox regression analyses of overall survival in 134 patients receiving chemoradiotherapy (CRT)

Variable	Comparator	Univariate analysis			Multivariate analysis		
		Exp(B)	95% CI	p Value	Exp(B)	95% CI	p Value
Female	Male	0.67	0.44 to 1.00	0.052	1.19	0.76 to 1.85	0.44
Age ≤65	>65	1.35	0.89 to 2.03	1.47	1.26	0.80 to 2.00	0.31
Ever-smoker	Never-smoker	1.23	0.57 to 2.67	0.59	0.89	0.40 to 1.97	0.78
ECOG PS ≤2	>2	0.86	0.43 to 2.02	0.86	1.20	0.54 to 2.67	0.65
Nonsquamous	Squamous	1.64	0.99 to 2.71	0.053	0.76	0.45 to 1.29	0.32
cCRT	sCRT	1.94	1.15 to 3.25	0.01	0.69	0.32 to 1.49	0.35
Tumour ≤3 cm	>3 cm	1.80	1.15 to 2.83	0.01	0.63	0.39 to 1.00	0.05
N1/N2, single-station	N2, multi-station, or N3	2.26	1.46 to 3.52	<0.001	0.39	0.21 to 0.74	<0.004

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; cCRT = concurrent CRT; sCRT = sequential CRT.



	Median (mo)	95% Confidence Interval	
		Lower bound	Upper Bound
N1/N2 single station [—]	28.567	18.517	36.616
N2 multistation/N3 [---]	11.633	9.869	13.398
Overall	18.567	12.357	24.776
Log Rank (Mantel-Cox) < 0.001			

FIGURE 6 Overall survival of patients with N1/N2 single-station nodal involvement compared with N2 multi-station or N3 nodal involvement from the start of radiotherapy (RT).

The multivariate analysis of survival demonstrated that tumour size and nodal station involvement were the only factors predictive of survival in patients treated with CRT (Table III).

In patients who would have been eligible for treatment with durvalumab according to the PACIFIC trial criteria ($n = 104$), median OS was 21.9 months (95% confidence interval: 12.3 months to 31.4 months).

Safety

Table IV lists emergency room visits for complications during and after CRT. In 30 patients (22.4%), 48 complications were observed. The most common reasons for emergency room visits were radiation complications, infections (pulmonary and other), fatigue, and pain. The rate of

TABLE IV Reasons for emergency room visits

Reason	Patients	
	(n)	(%)
Radiation pneumonitis	12	25
Infections		
Pulmonary (pneumonia)	9	18.7
Others (abscess, cellulitis, endocarditis)	4	8.0
Fatigue	6	12.4
Pain	5	10.4
Radiation esophagitis	3	6.2
PE or DVT	3	6.2
Febrile neutropenia	3	6.2
Pleural effusion	3	6.2
TOTAL	48	100.0

PE = pulmonary embolism; DVT = deep vein thrombosis.

complications was not different for concurrent (22%) and sequential (20%) treatment.

DISCUSSION

The results of this observational study provide a description of treatment patterns in an academic centre and reveal that the treatment of unresectable stage III NSCLC in general was in line with guidelines^{16,17}. To our knowledge, the present report is the first of a real-world experience from Quebec. According to the Canadian Cancer Registry, the incidence of stage III cancer ranges from 13% to 23% in various provinces¹⁸. Approximately 88% of patients with stage III NSCLC present with disease that is not amenable to curative resection¹⁹, similar to the rate seen in our study population. The Canadian Cancer Society team recommends the use of CRT for patients with inoperable stage III disease, a good performance status (ECOG 0–2), minimal weight loss, good pulmonary reserve, and tumour and anatomic confirmation, permitting radical-dose radiation without expected severe normal-tissue toxicity^{18,20}. Curative-intent CRT was

given to 59% of the patients with unresectable stage III NSCLC in our study, which is similar to data from Cancer Care Ontario^{21,22}. From 2010 to 2013 in Ontario, 48% of patients with inoperable lung cancer received curative-intent combined CRT, with a regional variation of 31%–63%^{23–25}.

Our results revealed that median OS in patients treated with combined CRT was 18.6 months. Based on the log-rank test, a significant survival benefit accrued to patients treated using cCRT compared with sCRT. That survival benefit of cCRT over sCRT observed in univariate analysis was no longer present in the multivariate analyses. The most probable explanation for the loss of significance is selection bias: patients receiving cCRT were younger, with less bulky disease. This type of bias occurs often in retrospective cohort studies and is usually controlled with Cox regression analysis²⁶.

The West Japan Lung Cancer Group²⁷ and Radiation Therapy Oncology Group 9410²⁸ studies both compared cCRT with sCRT. Both trials demonstrated modest survival improvements in favour of cCRT. Auperin *et al.*¹⁰ observed a significant benefit of cCRT (hazard ratio: 0.84; $p = 0.004$) compared with sCRT. However, in all of the foregoing studies, the survival benefit came at the expense of higher treatment toxicity, which was reported to be almost a 3–4 times that with sequential therapy. Our study failed to demonstrate the higher rate of toxicity in the cCRT group compared with the sCRT group, possibly because 37% of the cCRT group received gemcitabine–paclitaxel chemotherapy concurrent with radiation after 2 cycles of platinum-based induction therapy, which is the accepted chemotherapy regimen in Quebec. According to the latest guidelines from the American Society for Radiation Oncology, the optimal chemotherapy regimen for combined CRT is not known, given a paucity of randomized trials comparing various chemotherapy regimens in the setting of locally-advanced NSCLC¹⁶. The most commonly used regimens are combined cisplatin–etoposide and weekly carboplatin–paclitaxel. More recently, pemetrexed–cisplatin has been more prevalent in patients with nonsquamous NSCLC.

A small proportion of our patients (10%) died from causes other than lung cancer, which is consistent with the 14% reported by Souza *et al.*²⁹. Disease-specific survival was better when those patients were excluded.

Of our patients with unresectable stage III NSCLC, 78% would have been eligible to receive consolidation therapy with durvalumab, which is similar to the 70% reported by Sakaguchi *et al.*³⁰. Those patients had an OS of 21.9 months compared with 18.6 months for the cohort overall. Based on Cox regression analysis, the number of involved lymph nodes and the size of the primary tumour significantly affected survival. Combined CRT has the potential to offer patients with N1 or single-station N2 disease and a smaller primary tumour the combined benefits of improved local and distant disease control.

As in any retrospective cohort study, eliminating the possibility of selection bias is challenging. However, it appears that our study cohort is representative of the entire population of patients with unresectable stage III NSCLC treated at our institution. The study relies on data already collected, and therefore any systematic errors occurring during the chart abstraction process cannot be captured.

The 7th edition of the TNM staging system was used in our study. That system excludes patients with stage II disease who would have migrated to stage III under the 8th edition of TNM staging³¹. Another limitation of the study would be the lack of positron-emission tomography imaging, proper mediastinal staging at the time of diagnosis, and tumour differentiation (grade). Novel treatments such checkpoint inhibitors or durvalumab maintenance therapy were not available at the time of the study. Also, the study was limited to a single centre in Quebec.

CONCLUSIONS

Combined CRT has been the standard treatment for unresectable stage III NSCLC. In our study, a trend of better survival was seen for cCRT compared with sCRT. Factors predictive of survival in patients with stage III disease treated with CRT were tumour size and nodal station. New immuno-oncology treatments after standard cCRT for unresectable stage III NSCLC are the new standard in a select group of patients as defined by the eligibility criteria for the PACIFIC trial. Most patients with stage III disease would potentially be eligible for durvalumab maintenance therapy. Although the results from the study help to further contextualize the results from randomized controlled trials, the use and effectiveness of novel treatments have to be further studied in our patient population and similar real-world patient populations.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: MH and RNW are employees of AstraZeneca Canada. The remaining authors have no conflicts to disclose.

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