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Retrospective cohort study of unresectable stage III non-small-cell lung cancer in Canada

S.J. Seung HonBSc,* M. Hurry MSc MSc,† R.N. Walton MPH,† and W.K. Evans MD‡

ABSTRACT

Background The management of unresectable stage III non-small-cell lung cancer (NSCLC) is complex and best determined through multidisciplinary consultation. A longitudinal, population-level study was carried out to describe the management approach and outcomes of treatment in the real-world setting in Ontario.

Methods Individuals diagnosed with NSCLC between 1 April 2010 and 31 March 2015 were identified in the Ontario Cancer Registry. Unresectable disease was defined as no surgery reported within 3 months of diagnosis. Initial treatments included radiotherapy (RT, curative or palliative), chemotherapy, targeted therapy, and chemoradiation [CRT, concurrent (cCRT) or sequential (sCRT)]. Survival was calculated from diagnosis with stage III disease to death or last follow-up.

Results Of the 24,729 individuals diagnosed with NSCLC, 5243 (21.2%) had stage III disease, with most of the latter group (4542, 86.6%) having unresectable disease. Median age was 70 years, and 54.2% were men. The frequency of first-line treatment was cCRT, 22.1%; palliative RT, 21.0%; curative RT, 19.6%; no treatment, 19.6%; chemotherapy alone, 11.6%; sCRT, 5.4%; and targeted therapy, 0.7%. Median overall survival (mOS) was 14.2 months [95% confidence interval (CI): 13.6 months to 14.7 months], with the longest survival observed in patients who received targeted therapy (mOS: 34.7 months; 95% CI: 21.4 months to 51.2 months), and the poorest, in those receiving no cancer treatment (mOS: 5.9 months; 95% CI: 5.0 months to 6.4 months). The mOS in patients receiving cCRT was 23.6 months (95% CI: 21.4 months to 25.6 months).

Conclusions Guideline-recommended cCRT is undertaken in only a small proportion of patients with unresectable NSCLC in Ontario. The reasons for low uptake of that recommendation are only partly understood.

Key Words Lung cancer, unresectable stage III disease, real-world evidence

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BACKGROUND

Lung cancer is the most commonly diagnosed cancer in Canada, and given that an average of 78 individuals are diagnosed every day, the disease remains the leading cause of cancer-related death in the country[1]. Approximately 23%–41% of patients with lung cancer present with stage III disease[2–7]. Stage III non-small-cell lung cancer (NSCLC) is a heterogeneous disease, ranging from resectable tumours with occult microscopic nodal metastases to unresectable tumours with extensive lymph node involvement, but with no evidence of distant metastases[8]. For patients with unresectable stage III NSCLC, the evidence-based guideline from Ontario Health (Cancer Care Ontario) [OH(CCO)] recommends treatment with platinum-based doublet chemotherapy in combination with radiotherapy (CRT) administered with curative intent either concurrently (cCRT) or sequentially (sCRT)[9]. Curative-intent radiotherapy (RT) should be administered at a dose of 60–66 Gy in daily fractions over 6 weeks[10]. Patients undergoing this treatment must have a good performance status and should not have experienced significant weight loss[9].

The 5-year overall survival (OS) for patients with lung cancer varies by stage. In Canada, the 5-year OS is 58%–73% for stage IA, 15% for stage III treated with cCRT, 11% for stage III treated with sCRT, and 2%–13% for stage IV[11].

Correspondence to: Soo Jin Seung, 2075 Bayview Avenue, Room E240, Toronto, Ontario M4N 3M5.
E-mail: soojin.seung@sunnybrook.ca ■ **DOI:** https://doi.org/10.3747/co.27.6047

In a U.S. study, 12% and 9% of patients treated with cCRT and sCRT respectively were alive without progressing to metastatic disease for at least 5 years after treatment[12]. Although patients with stage III disease can be treated with curative intent, many will either experience locoregional recurrence or develop distant metastases[13]. As a result, OS remains poor.

In recent years, treatment options have increased for patients with advanced NSCLC, with the emergence of therapies that target molecular abnormalities or the complex interaction between tumour cells and the immune system. Given the results of the PACIFIC trial evaluating durvalumab, an anti–PD-L1 antibody, for unresectable stage III NSCLC, the use of an immunotherapy strategy is of particular relevance to disease management in the affected population. Patients received durvalumab after completion of at least 2 cycles of cCRT for a maximum of 12 months[14,15]. The PACIFIC trial demonstrated a statistically significant and clinically meaningful increase in progression-free survival and OS. Median duration of progression-free survival was 17.2 months [95% confidence interval (CI): 13.1 months to 23.9 months] in the durvalumab group compared with 5.6 months (95% CI: 4.6 months to 7.7 months) in the placebo group[15]. At data cut-off (March 2018), median OS (mOS) was not reached (95% CI: 34.7 months to not reached) in the durvalumab group; it was 28.7 months (95% CI: 22.9 months to not reached) in the placebo arm. Further, the proportions of patients alive at 12 months (83.1% vs. 75.3%) and at 24 months (66.3% vs. 55.6%) were substantially higher with durvalumab than with placebo[15].

Few studies in Canada have reported the proportion of patients with stage III NSCLC treated with guideline-recommended therapy. The aim of the present study was to better understand the clinical characteristics, treatment patterns, and outcomes of patients with stage III NSCLC treated in the province of Ontario.

METHODS

Patients diagnosed with NSCLC in the province of Ontario between 1 April 2010 and 31 March 2015, with follow-up to 31 March 2017, were identified in the Ontario Cancer Registry (OCR) based on the *International Classification of Diseases for Oncology*, 3rd edition, with relevant morphology codes. Patients were excluded if they had a 2nd primary cancer within 3 years before or after the NSCLC diagnosis, an unknown disease stage, or less than 1 year of available follow-up information.

Data Sources

Ontario has a population of 14 million and provides publicly funded health care services through OHIP (the Ontario Health Insurance Plan). To generate real-world data, ICES collects OHIP and other population-level health information.

To determine the trajectory of patient care over time, health information for each individual patient was linked to applicable datasets. For patients with NSCLC, linkages were made to the following 13 datasets: the OH(CCO) Activity Level Reporting (ALR) database, the Continuing Care Reporting System, the Home Care Database, the Discharge Abstract Database, the National Ambulatory Care Reporting System, the National Rehabilitation Reporting System, the New Drug Funding Program (NDFP), the Ontario Cancer Registry, the Ontario Drug Benefit (ODB) program, OHIP, the Ontario Mental Health Reporting System, and the Registered Persons Database. The Registered Persons Database contains demographic information about all individuals with OHIP coverage (for example, date of birth, date of death). The National Ambulatory Care Reporting System database reports the number of ambulatory cancer clinic visits at any health care facility in Ontario based on visit dates. The OHIP database captures physician visits and fees for health professionals, including general practitioners, medical and radiation oncologists, and other specialists. Inpatient rehabilitation services required for care before and after lung surgery are captured in the National Rehabilitation Reporting System. Three databases were used to determine treatments received by the study cohort: the ODB, NDFP, and ALR. The ODB program database contains documentation about all oral medications, including molecularly targeted therapies and a wide range of supportive care drugs (for example, analgesics and antiemetics), prescribed to individuals 65 years of age and older or to those receiving social assistance. The NDFP captures most of the intravenous systemic chemotherapy agents that are publicly funded by OH(CCO), except for inexpensive older agents. If treatment information was not available in either the ODB or the NDFP, treatment information from the ALR database was used. The ALR database captures patient-level activity relating to radiotherapy and chemotherapy.

Information about comorbidities was captured using two tools: the Charlson comorbidity index[16], which includes 17 conditions and uses the diagnosis codes from the *International Statistical Classification of Diseases and Related Health Problems* recorded during inpatient hospitalizations in the 5 years preceding the NSCLC diagnosis, and the Johns Hopkins (Baltimore, MD, U.S.A.) Aggregated Diagnosis Groups[17], which include 32 morbidity groups and capture diagnostic codes during outpatient health system encounters in the 2 years preceding the NSCLC diagnosis. The Aggregated Diagnosis Groups were also assigned to a simplified morbidity category called "predicted resource utilization bands." Conversion of each individual's postal code using Statistics Canada's Postal Code Conversion File allocated that individual to 1 of 5 neighbourhood income quintiles.

Study Variables, Assessment of Outcomes, and Statistical Analyses

Descriptive statistics were used to evaluate treatment patterns in the study cohort. Patients with stage III NSCLC were considered to have unresectable disease if no documentation of a surgical resection was found within 3 months of diagnosis. Radiotherapy was defined as either radical (curative) or palliative based on recorded treatment intent, body region treated, dose per fraction, and number of fractions. Monotherapy and doublet drug regimens are reported as chemotherapy alone. Any overlap in the administration of RT and chemotherapy was defined as cCRT, and sCRT was defined as RT and chemotherapy that did not overlap, but that were administered within 30 days of each other. In patients receiving first-line cCRT and in patients who received at least 2 cycles of chemotherapy, further analyses were carried out

for second-line treatments. Targeted therapies included the oral tyrosine kinase inhibitors afatinib, erlotinib, and gefitinib. Patients were categorized as having received no treatment if no treatment information was reported or if the patient died before receiving any treatment.

The SAS Enterprise Guide software application (version 7.15: SAS Institute, Cary, NC, U.S.A.) was used for the analysis. Patient and disease characteristics are presented as numbers and percentages for categorical variables and as means with standard deviation for continuous variables. Treatment patterns are presented as the numbers and percentages of patients receiving various types of treatment.

Survival is reported as OS and mOS. Kaplan–Meier survival curves were constructed starting at the date of diagnosis and continuing to death (for those with a known date of death); otherwise, patients were censored. Curves were stratified by resected or unresectable disease, and type of first-line treatment. Kaplan–Meier curves were compared using log-rank tests. All outcomes are reported at an aggregate level, and all analyses were conducted by the ICES Data and Analytic Services analyst.

Ethics Review

Our study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre.

RESULTS

Baseline Characteristics

Over a 5-year period, of 24,729 individuals diagnosed with NSCLC, 21.2% (n = 5243) had stage III disease, with 86.6% of those stage III patients (n = 4542) having unresectable disease. As shown in Table I, median age in that group was 70 years, slightly more than half were men (54.2%), and most had been diagnosed with stage IIIA disease (62.4%). Mean score on the Charlson comorbidity index was 1.0 ± 1.5, and more than half the patients (>51%) had an Aggregated Diagnosis Groups score in the 5–9 range or greater, corresponding to moderate-to-high utilization of health care resources, likely because of comorbidities. In terms of income, 46.3% of the patients fell into the two lowest income quintiles.

Treatment Patterns

Of the 4542 patients with unresectable stage III disease, all were referred to at least 1 specialist during the study period (90.8% to a radiation oncologist, 67.5% to a medical oncologist). Upon diagnosis, 64.2% of the cohort with unresectable disease received therapy within 3 months; 19.6% received no treatment. Of the 34 patients who received targeted therapies, only half received first-line targeted therapy within 3 months of diagnosis (n = 17). Figure 1 shows that a substantial proportion of patients (40.6%) received either no treatment (19.6%) or palliative RT only (21.0%). Less than one third of the cohort received guideline-recommended treatment [1002 patients (22.1%) received cCRT, and 247 (5.4%) received sCRT]. Of the 1002 patients who received first-line cCRT, a large proportion (46.1%) received no additional treatment, but when second-line treatments were used, 19.0% received RT, 12.4%

TABLE I Baseline characteristics of a patient cohort (n = 4542) with unresectable stage III non-small-cell lung cancer[a]

Variable	Value
Age (years)	
Median	70
IQR	63–77
Sex [*n* (%)]	
Women	2080 (45.8)
Men	2462 (54.2)
Stage [*n* (%)]	
IIIA	2833 (62.4)
IIIB	1579 (34.8)
III (subcategory unknown)	130 (2.9)
Mean score on the CCI	1.00±1.46
Comorbidities in 3147 patients [*n* (%)]	
COPD	535 (17.0)
Diabetes with complications	330 (10.5)
Diabetes without complications	244 (7.8)
Myocardial infarction	229 (7.3)
CHF	215 (6.8)
CVD	127 (4.0)
Renal disease	93 (3.0)
Peptic ulcer disease	80 (2.5)
Dementia	33 (1.0)
Connective tissue or rheumatic disease	29 (0.9)
Metastatic cancer	22 (0.7)
Mild liver disease	22 (0.7)
Hemiplegia or paraplegia	14 (0.4)
Moderate or severe liver disease	11 (0.3)
Mean ADGs[b]	7.9±3.6
ADG category [*n* (%)]	
0–4	777 (17.1)
5–9	2295 (50.5)
11–14	1281 (28.2)
15+	189 (4.2)
Predicted RUB [*n* (%)]	
Non-users	42 (0.9)
Healthy users	40 (0.9)
Resource utilization [*n* (%)]	
Low	119 (2.6)
Moderate	1663 (36.6)
High	1468 (32.3)
Very high	1210 (26.6)
Census-based income quintile [*n* (%)]	
1 (lowest)	1102 (24.3)
2	989 (21.8)
3	869 (19.1)
4	864 (19.0)
5 (highest)	699 (15.4)
Missing	19 (0.4)

[a] Of these patients, 601 underwent resection.
[b] Johns Hopkins, Baltimore, MD, U.S.A.

IQR = 25%–75% interquartile range; CCI = Charlson comorbidity index; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; CVD = cerebrovascular disease; ADGs = Aggregated Diagnosis Groups; RUB = resource utilization band.

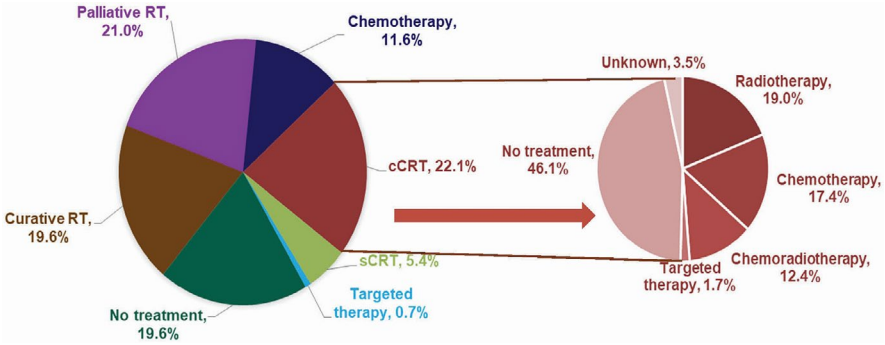


FIGURE 1 Left panel: First-line treatment distribution for unresectable stage III non-small-cell lung cancer (n = 4542). Right panel: Second-line treatment distribution for the group initially receiving concurrent chemoradiotherapy (cCRT, n = 1002). RT = radiation therapy; sCRT = sequential chemoradiotherapy.

received CRT, and 17.4% received chemotherapy alone. Use of targeted therapy was minimal.

Of patients receiving first-line cCRT, 97% (n = 967) completed 2 or more cycles, and 505 of them went on to receive second-line treatment upon disease progression. At the time of analysis, 189 (19.5%) were alive, but had not received second-line treatment, and 273 (28.2%) had died before receiving second-line treatment. The median time from the 2nd chemotherapy cycle in first-line cCRT to initiation of second-line treatment in the 505 patients was 155 days (range: 1–1726 days).

Survival

Survival was longest in patients who received targeted therapy (n = 34; mOS: 34.7 months; 95% CI: 21.4 months to 51.2 months), followed by those who received cCRT (mOS: 23.6 months; 95% CI: 21.4 months to 25.6 months), curative RT (mOS: 17.0 months; 95% CI: 15.6 months to 18.5 months), chemotherapy alone (mOS: 16.5 months; 95% CI: 14.8 months to 17.9 months), sCRT (mOS: 14.4 months; 95% CI: 11.9 months to 17.9 months), palliative RT (mOS: 7.1 months; 95% CI: 6.6 months to 7.6 months), and no treatment (mOS: 5.9 months; 95% CI: 5.0 months to 6.4 months; Figure 2).

The mOS for the total stage III cohort (n = 5243) was 14.2 months (95% CI: 13.6 months to 14.7 months). The mOS for the unresectable group was 12.9 months (95% CI: 12.4 months to 13.4 months) compared with 39.9 months (95% CI: 34.7 months to 50.1 months) for the group that underwent surgical resection (Figure 3, $p < 0.001$).

At the time of the survival analysis, 17.5% of patients in the unresectable arm and 44.9% of the patients who underwent tumour resection were censored. Survival at 1, 2, 3, 4, and 5 years for the patients with unresectable stage III disease was 52.6%, 30.7%, 21.5%, 17.0%, and 14.8% respectively. For the subset of patients who received at least 2 cycles of cCRT, mOS was 21.3 months, and the survival rate at 1, 2, 3, 4, and 5 years was 69.0%, 45.9%, 33.4%, 29.1%, and 25.6% respectively.

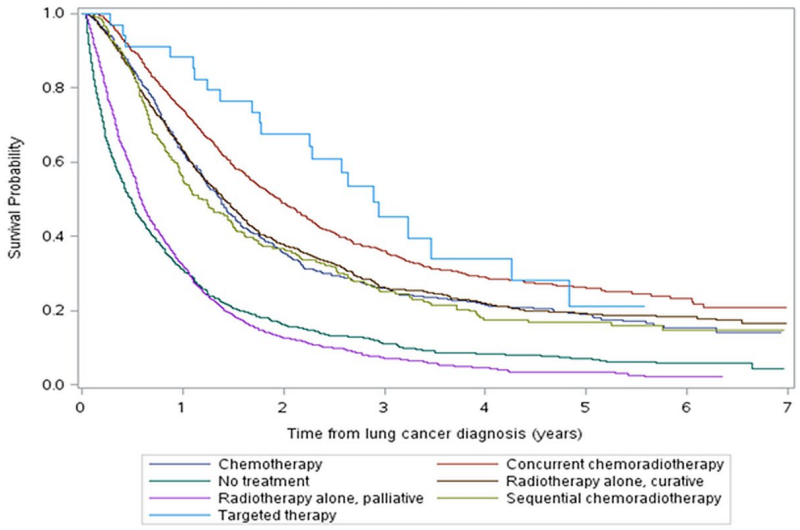
DISCUSSION

This study provides a population-level perspective on the treatment approaches used to manage stage III NSCLC in Ontario. Our study identified 5243 individuals diagnosed with stage III NSCLC over a 5-year period, representing 21% of the overall NSCLC population, which is in line with previously published studies reporting on stage distribution[2,18]. Similarly, the 86.6% of patients considered to be unresectable in our study was comparable to the proportion seen in a B.C. study, in which approximately 88% of patients with stage III NSCLC presented with disease that was not amenable to curative resection[19].

Although cCRT is considered the guideline-recommended standard of care for unresectable stage III NSCLC[9,12,20,21], our study found that only 22.1% of our real-world cohort received cCRT. In one B.C. study[19], only 12.3% of patients diagnosed with stage III disease between 2000 and 2007 were treated with cCRT. Another B.C. study involving 3869 patients with stages I–III disease reported that only 1658 (43%) received curative-intent therapy[9]. Similarly, a population-based study from Alberta found that only 11.7% of patients with unresectable stage III disease received cCRT[22]—a proportion lower than that in a prior study from Alberta which reported that 18% of patients received cCRT between 2005 and 2007[23].

The reasons that use of cCRT was not higher in the Ontario cohort are largely unknown. Approximately 10% of patients were not referred to either a radiation or a medical oncologist. Information about Eastern Cooperative Oncology Group performance status, size and location of the tumour, or patient willingness to accept cCRT was not available. Patient choice and comorbidities might also have led to cCRT being bypassed. An Alberta study suggested that there are also barriers to treatment based on the patient's residence, with fewer referrals being made from rural settings to the urban centres that provide chemotherapy and RT treatments[23].

The linkages to administrative databases made it possible to assess clinical outcomes by treatment strategy. Although the databases did not include information about mutation status, we assumed that individuals who received first-line oral targeted therapy had actionable mutations and were treated with a tyrosine kinase inhibitor (afatinib, erlotinib, or gefitinib). Those patients had the best mOS, at 34.7 months (2.9 years), indicating the potential utility of targeted agents as any-line treatment for patients with unresectable stage III NSCLC. Patients who received first-line cCRT had a slightly shorter mOS of 23.6 months (2.0 years),



CTx	527	355	200	113	75	47	22	—
cCRT	1,002	770	513	276	147	76	34	7
None	889	297	154	87	45	26	14	—
RT								
Curative	890	595	351	222	145	97	51	9
Palliative	953	342	130	63	30	12	—	—
sCRT	247	150	91	57	36	23	11	—
Targeted therapy	34	30	23	13	6	—	—	—

FIGURE 2 Kaplan–Meier survival curves for patients with unresectable stage III non-small-cell lung cancer by first-line treatment. CTx = chemotherapy; cCRT = concurrent chemoradiotherapy; RT = radiotherapy; sCRT = sequential chemoradiotherapy.

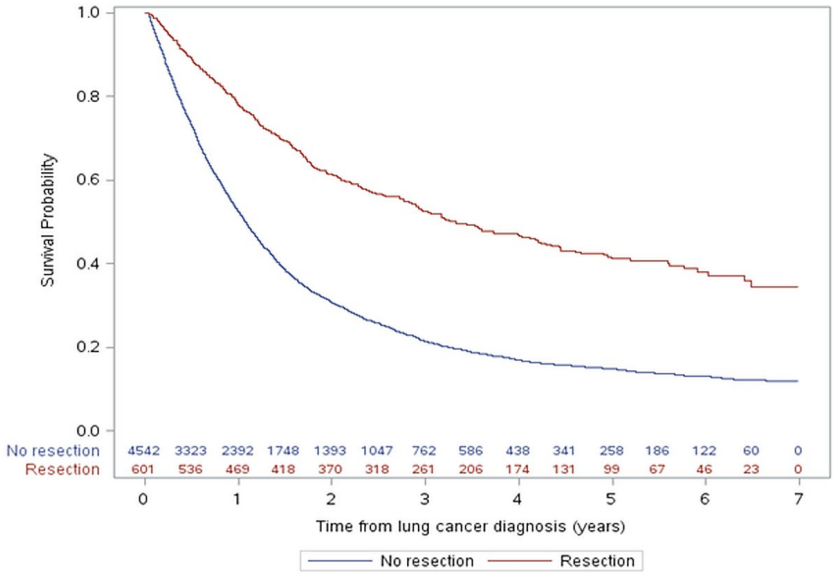


FIGURE 3 Kaplan–Meier survival curves for patients with stage III non-small-cell lung cancer by resection status (yes, *n* = 601; no, *n* = 4542).

which was superior to the mOS for individuals who received either curative RT (17.0 months) or chemotherapy alone (16.5 months).

The median age of patients receiving 2 or more cycles of cCRT was 66 years, which was similar to the median age of 64 years in the PACIFIC trial[15], but younger than the overall cohort, suggesting that selection for combined-modality therapy was made in part based on age.

The survival of patients receiving cCRT in our real-world cohort is of particular interest given the promise of immunotherapy in patients with unresectable disease who respond to or are stable after 2 or more cycles of cCRT[15]. In our cohort, the 967 patients who received 2 or more cycles of cCRT had a median survival of 21.3 months, and survival rates at 1, 2, and 3 years were 69.0%, 45.9%, and 33.4% respectively. In a naïve comparison with the results

from the recent PACIFIC study, survival rates at 1, 2, and 3 years were 74.6%, 55.3%, and 43.5% respectively[24]. The likely reasons for the higher survival rates in the control arm of the PACIFIC trial might include differences in patient characteristics (for example, Eastern Cooperative Oncology Group performance status) or confounding because of different subsequent therapies (for example, patients in the placebo arm receiving subsequent immunotherapies or targeted agents).

The PACIFIC study also reported that survival rates for those who responded to or were stable after 2 or more cycles of cCRT and then received durvalumab were 83.1% and 66.3% at 1 and 2 years respectively[15]. In the placebo arm of the START trial[25], which compared maintenance treatment using Muc1 antigen-specific immunotherapy with placebo in patients having unresectable stage III NSCLC who completed CRT, median survival in patients who received 2 or more cycles of cCRT was 20.6 months, with survival rates of 75%, 46%, and 37% at 1, 2, and 3 years respectively[24]. Those survival results strongly suggest that the new immunotherapy approach substantially improves survival for patients with unresectable NSCLC and could become a new standard of care. Those promising results might also help to change attitudes toward the treatment of NSCLC and result in a greater proportion of patients receiving combined-modality therapy (for example, cCRT) followed by immunotherapy.

Nonetheless, our study has several limitations. First, the use of targeted therapy in our study might be underreported, because in Ontario's publicly funded health care system, oral agents are funded and captured in the ODB database only for patients 65 years of age and older or for those who receive social assistance. In Ontario, oral agents for patients less than 65 years of age are covered either through private insurance or out-of-pocket payments and are therefore not captured in any public administrative database. A second limitation is that important information about disease characteristics (for example, histologic subtype) that would permit the interpretation of clinical outcomes is lacking. Although physicians routinely assess the performance status of their patients, that information, when captured, is not reported to the ICES databases and therefore cannot be assessed. Furthermore, information about other patient characteristics that influence the decision to treat using cCRT, including smoking status, size and location of the primary tumour, weight loss greater than 5%, and severe organ dysfunction that would preclude treatment (for example, pulmonary insufficiency, renal impairment) are not available. Details about whether a patient has been discussed at an multidisciplinary cancer conference and whether the treatment recommendation of that conference has been accepted by the treating physician are also not accessible. A third limitation is that it is not possible to determine from administrative data whether a patient has been advised to undergo combined-modality therapy, but has refused or been unable to attend for treatment because of logistics. It is anticipated that, given the real-world median age of patients with NSCLC, some older patients might choose not to undergo aggressive combined-modality therapy. Furthermore, Ontario is a very large province, and some patients might find it impossible to travel to and from regional treatment centres to receive such therapy.

CONCLUSIONS

This study of a large cohort of patients with unresectable stage III NSCLC in the province of Ontario demonstrated that the proportion of patients receiving standard-of-care treatment (cCRT) was only 22% over the study period. Survival outcomes were comparable to those in previously reported trials, including trials involving patients receiving cCRT before access to immunotherapies or targeted therapies became widespread. Our results could support health care decision-makers by characterizing the size of the patient population with unresectable stage III NSCLC, treatment patterns in that population, and long-term survival outcomes in the real-world setting.

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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: SJS received an unrestricted grant from AstraZeneca Canada Inc. to conduct this study. MH and RNW are employees of AstraZeneca Canada Inc. WKE has received fees as an advisory board member from AbbVie, Astellas, Bristol–Myers Squibb, Eisai, Gilead, Lilly, Takeda, and Merck, and consulting fees from AstraZeneca, Boehringer Ingelheim, Celgene, Janssen, Lilly, Roche, Servier, and Sanofi Genzyme.

AUTHOR AFFILIATIONS

*HOPE Research Centre, Sunnybrook Research Institute, Toronto, ON; †AstraZeneca Canada Inc., Mississauga, ON; ‡McMaster University, Department of Oncology, Division of Medical Oncology, Hamilton, ON.

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