ORIGINAL ARTICLE

Survival Outcomes of Salvage Therapy for Local and Regionally Recurrent NSCLC

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ABSTRACT

Introduction: The treatment of locally recurrent NSCLC after initial curative therapy is variable. We sought to perform a real-world analysis of curative and palliative therapeutic strategies used in locally recurrent NSCLC and explore the impact of baseline factors and the previous and recurrent treatment on outcomes.

Methods: A retrospective cohort study was done including all patients with stage I to III NSCLC who were referred to BC Cancer and received curative-intent therapy between 2005 and 2012. Patients were followed up to determine whether they developed locoregional recurrence. Two cohorts were created: curative-intent treatment at recurrence (surgery, radiotherapy with $\geq$50Gy $\pm$ chemotherapy, stereotactic radiosurgery) and palliative treatment. The primary outcome was overall survival (OS).

Results: A total of 1571 patients received curative-intent therapy during the study period. Of these, 179 (11%) developed a local and regional recurrence. A total of 51 patients (28%) were treated with curative intent at recurrence (12 surgery, 39 radiotherapy $\pm$ chemotherapy), and 128 (72%) received palliative treatment only. Patients receiving curative-intent therapy were more likely to have an Eastern Cooperative Oncology Group performance status of 0 to 1 (90% versus 58%), earlier stage at diagnosis (51% stage I) and receive more aggressive staging investigations at recurrence, pathologic confirmation (75% versus 27%) and positron emission tomography (77% versus 27%). OS was longer in the cohort receiving curative-intent therapy, with an OS of 34.3 months versus 9.8 months ($p < 0.001$) in palliative treatment.

Conclusions: In this real-world population, isolated locoregional recurrences occurred in 11% of patients. Curative-intent treatment at recurrence is associated with a reasonable chance of long-term survival, making aggressive therapy of locoregional recurrences an important treatment consideration.

Keywords: Salvage; Curative-intent; Recurrence; Real-world evidence; Radiotherapy; Surgery

Introduction

NSCLC is the leading cause of cancer death worldwide.[1] Approximately half of the patients present with locoregional disease, which is potentially amenable to curative-intent therapy.[2] A proportion of patients treated with curative intent will go on to develop an isolated local or regional recurrence. The exact incidence varies depending on the stage at diagnosis and type of initial curative therapy received; however, it is reported to range from 5% to 15%.[3–8]

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There is limited prospective evidence available to guide the treatment of locoregionally recurrent NSCLC. Patients with isolated pulmonary relapse can be treated with further local therapies, such as a surgical procedure or stereotactic radiosurgery (SRS).[9] Patients with isolated locoregional or regional relapse are often treated with radical doses of radiation therapy (RT), with or without chemotherapy, with estimated survival similar to de novo stage III disease.[7–12] It is not clear how many patients are eligible for treatment with curative intent at the time of recurrence.

Given the lack of prospective studies in this space, there is an ongoing need for real-world evidence to optimize therapy in this group of patients. We proposed a population-based review of patients with NSCLC, with the objective of evaluating the rates of isolated locoregional recurrence, treatment patterns, and their influence on survival.

Materials and Methods

Population

A retrospective review of all patients with stage I to III NSCLC referred to BC Cancer from January 2005 to December 2012 was performed. BC Cancer is a provincial cancer program that serves a population of 5.1 million. Approximately 80% of patients with advanced lung cancer in the province of British Columbia are referred to BC Cancer. All referred patients are registered in the Outcomes and Surveillance Integration System, a database that houses the Lung Tumor Outcomes group. The database records baseline disease characteristics and patient demographics. Patients receiving curative-intent therapy (surgical procedure or radiotherapy ± chemotherapy) were followed up to determine whether they developed an isolated local and regional recurrence, defined as disease confined to the thorax and classified as M0 on the basis of the American Joint Committee on Cancer, eighth edition. Local recurrence refers to a disease in the lung parenchyma, whereas regional recurrence refers to a disease in regional lymph nodes. Recurrence was determined by a retrospective review of electronic records through BC Cancer's Cancer Agency Information System. Clinical follow-up and imaging investigations were performed at the discretion of the treating physician.

Data Collection

Information on known prognostic factors was collected through Outcomes and Surveillance Integration System. Treatment details at the time of local recurrence were collected by retrospective review. Two cohorts were created: those receiving curative-intent therapy at recurrence (surgical procedure or radiotherapy), and those receiving palliative therapy.

Curative-intent therapy at recurrence was defined as any of the following: (1) a surgical procedure with curative-intent, (2) SRS, or (3) radiotherapy greater than or equal to 50 Gy plus or minus chemotherapy.

The date of death was verified by the BC Cancer Surveillance and Outcome unit or obtained from BC Vital Statistics Agency or Statistics Canada, which registers all deaths that occur in the province and country.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software version 23. Known prognostic factors were compared between cohorts using the chi-square or Fisher's exact test, whichever was appropriate (categorical variables), or the Mann-Whitney test (continuous variables). A p value of 0.05 was considered statistically significant.

The primary outcome measure was overall survival (OS) from the date of diagnosis of recurrent disease. OS was estimated using the Kaplan-Meier method. Patients were censored by the date of the last clinical encounter or investigation confirming the patient was alive. Survival curves were compared using the log-rank test. Multivariate analysis of potential factors associated with OS was performed using the Cox proportional hazards model.

Exploratory analyses were performed to compare OS for different curative modalities and survival for patients with a local-only versus locoregional relapse.

Ethics Statement

This study received approval from the local institutional research ethics board (University of British Columbia—BC Cancer Research Ethics Board; H15-02509), and approval was given for a waiver of consent to extract and analyze the archival data from the database.

Results

Rate of Isolated Locoregional Recurrence

A total of 1571 patients with stage I to III NSCLC were referred to BC Cancer during the study period and treated with curative-intent therapy. Of these, 179 (11%) went on to develop isolated local and regional recurrence, and 632 (40%) had metastatic recurrence. Therefore, our final population of interest included 179 patients (Fig. 1).

Baseline Patient Characteristics

Of the 179 patients who developed an isolated locoregional recurrence, 51 (28%) received curative-intent treatment at recurrence, and the remaining 128 (72%) received palliative-intent treatment (Fig. 1). The

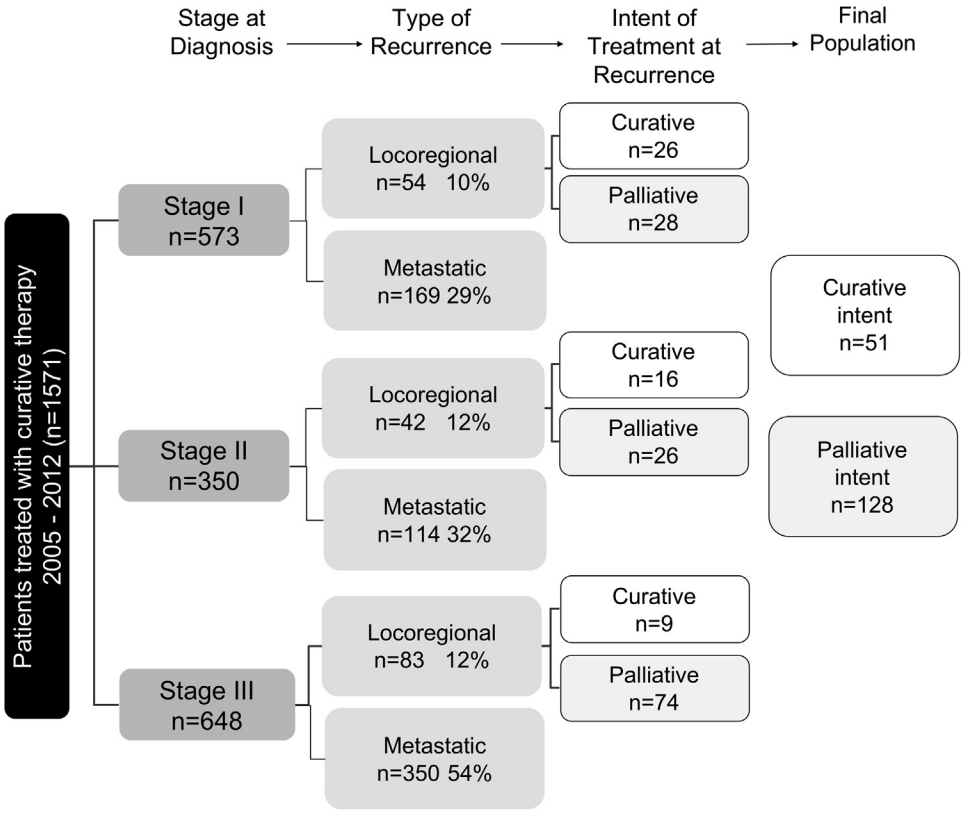

Figure 1. Population consort diagram.

baseline characteristics of patients at the time of their initial diagnosis are presented in Table 1. In the overall population, the median age was 68 years; 49% were women; 46% had adenocarcinoma, 36% had squamous cell carcinoma, and 18% were classified as other or not otherwise specified; 30% had stage I, 24% had stage II, and 46% had stage III disease; 9% were never-smokers; 50% had surgical intervention as initial

Table 1. Baseline Characteristics at Initial Presentation

Characteristic		Curative-intent at Recurrence n = 51, n (%)	Palliative Treatment at Recurrence n = 128, n (%)	*p* Value
Age at initial diagnosis, y	Median	68	68	0.886
	(range)	48-83	42-89	
Sex	Female	27 (53)	61 (48)	0.523
	Male	24 (47)	67 (52)	
Histologic subtype	Adenocarcinoma	29 (57)	54 (42)	0.150
	Squamous	13 (26)	51 (40)	
	NOS/other	9 (18)	23 (18)	
Stage at initial diagnosis	I	26 (51)	28 (22)	<0.001
	II	16 (31)	26 (20)	
	III	9 (18)	74 (58)	
Smoking status	Never	4 (8)	12 (9)	0.806
	Former	24 (47)	52 (41)	
	Current	23 (45)	63 (49)	
	Unknown	0 (0)	1 (1)	
Initial Curative Therapy	Surgery	41 (80)	49 (38)	<0.001
	RT	10 (20)	72 (56)	
	Both	0 (0)	7 (6)	
Chemotherapy curative-intent	No	30 (59)	54 (42)	0.044
	Yes	21 (41)	74 (58)	

Note: Values are presented as n (%) unless otherwise indicated. Never-smokers were defined as those who had less than 100 cigarettes over lifespan; former smokers were defined as those who quit greater than 1 year ago; current smokers were defined as actively smoking or quit less than 1 year ago.
NOS, not otherwise specified; RT, radiation therapy.

therapy, 46% had radiation, and 4% had both. There were statistically significant differences between the cohorts of patients receiving curative or palliative therapy with respect to the stage at initial diagnosis ($p < 0.001$) and the type of initial treatment given ($p < 0.001$). Biomarker testing was not available for most patients (73% EGFR unknown, 82% ALK unknown).

Patient Characteristics at the Time of Locoregional Recurrence

The median time from the initial diagnosis to the development of recurrent disease was 15.3 months. The details regarding recurrent disease are presented in Table 2. In the overall population, the median age was 69 years; 67% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; 48% had local relapse, 26% had regional relapse, and 26% had both; 41% received positron emission tomography (PET) scan at recurrence; and 41% received pathologic confirmation of recurrent disease. Patients treated with curative intent at recurrence were more likely to have good ECOG PS, have lower T stage at relapse, and receive pathologic confirmation and PET scanning at the time of recurrent disease.

Treatment of Recurrent Disease

Of the 51 patients receiving curative-intent therapy at relapse, 12 (24%) had surgical intervention, 16 (31%) chemoradiation, and 23 (45%) radical radiation alone. Surgical therapy included four wedge resections, seven lobectomies, and one pneumonectomy, with one patient receiving adjuvant chemotherapy. Radiotherapy doses included SRS in five (13%) patients, 50 to 59 Gy for 13 (33%), and greater than or equal to 60 Gy for 21 (54%). Fourteen of 21 patients (67%) who were treated with greater than or equal to 60 Gy received concurrent or sequential chemotherapy, compared with two of 13 patients (15%) treated with 50 to 59 Gy.

For the 128 patients receiving palliative-intent therapy at relapse, 56 patients (44%) received local radiotherapy less than 50 Gy, and 55 had systemic therapy (43%). The rationale for receiving palliative treatment only is presented in Figure 2. The most common reason was because of a previous high-dose radiotherapy resulting in issues with overlapping RT fields.

Overall Survival

At the time of analysis, 161 patients (90%) had died. The median OS from the time of diagnosis of the recurrent disease in the entire population was 13.0 months. The median OS was significantly longer at 34.3 months in the cohort treated with curative-intent therapy, compared with 9.8 months in those receiving palliative treatment, with a hazard ratio (HR) of 0.33 (95% confidence interval [CI]: 0.23–0.48) (Fig. 3*A*). Similarly, the 5-year OS was longer at 29.9% (95% CI: 15.7–44.1) for curative therapy compared with 3.4% (95% CI: 0–6.8) for palliative therapy.

In sensitivity analysis, there remained a significant difference in OS when the analysis was restricted only to patients with PET scan at recurrence (median OS 33.1 mo curative versus 18.4 mo palliative) or those with pathologic confirmation of disease (median OS 38.3 mo curative versus 13.4 mo palliative).

For the 51 patients receiving curative therapy, those undergoing surgery (median OS 38.3 mo), SRS (57.9 mo), or radiotherapy greater than or equal to 60 Gy (34.5 mo) had similar survival outcomes (Fig, 3*B*). Patients receiving RT at 50 to 59 Gy had inferior outcomes with a median OS of 11.8 months.

Table 2. Characteristics at Time of Recurrent Disease

Characteristic		Curative-intent at Recurrence n = 51, n (%)	Palliative Treatment at Recurrence n = 128, n (%)	*p* Value
Age at recurrent diagnosis, y	Median	69	70	0.538
	(range)	49-85	43-92	
Time to recurrence (mo)	Median	17.7	15.0	0.298
	(range)	3.5-72.7	1.1-92.9	
ECOG at recurrence	0-1	46 (90)	74 (58)	<0.001
	≥2	5 (10)	47 (37)	
	Unknown	0 (0)	7 (6)	
Distribution of recurrent disease	Local	31 (61)	55 (43)	0.041
	Regional	13 (26)	34 (27)	
	Both	7 (14)	39 (31)	
Pathologic confirmation	No	13 (26)	93 (73)	<0.001
	Yes	38 (75)	35 (27)	
PET scan at recurrence	No	12 (24)	93 (73)	<0.001
	Yes	39 (77)	35 (27)	

Note: Values are presented as n (%) unless otherwise indicated.
ECOG, Eastern Cooperative Oncology Group; PET, positron emission tomography.

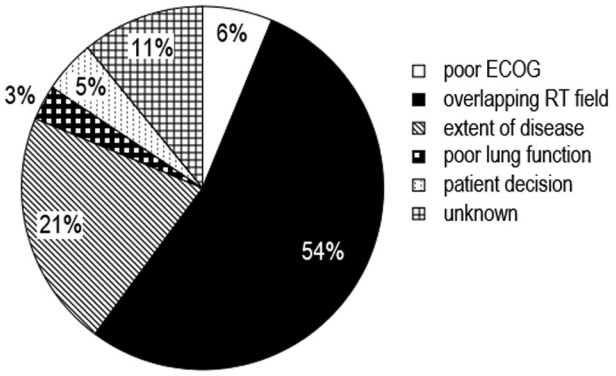

Figure 2. The rationale for noncurative therapy in the locally recurrent group. ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy.

Univariate and Multivariate Analysis for OS

In univariate analysis, nonsquamous histologic subtype, never-smoking status, ECOG PS 0 to 1, stage I at initial diagnosis, and local recurrence were associated with improved OS (Table 3). On comparison of treatment cohorts, palliative therapy was inferior to curative therapy (HR: 3.02). ECOG PS, stage at diagnosis, type of recurrence event, and treatment cohort were included in the multivariate model. In this model, all variables remained significant. Compared with patients presenting with stage I disease at the time of initial diagnosis, those with stage II disease had similar survival after recurrence (HR: 1.00); however, those with initial stage III disease had significantly worse outcomes (HR: 1.76). The effect of treatment cohort (curative versus palliative intent) was attenuated in the multivariate model (HR: 2.31); however, it remained significant (95% CI: 1.53–3.51).

Discussion

In a large population-based study, we found that isolated local and regional relapses were rare overall; nevertheless, it still represents a significant number of patients given the high burden of NSCLC worldwide.[1] A total of 28% of patients were eligible for curative-intent therapy at relapse and had a median survival of 34.3 months. This is similar to that in previously reported studies indicating survival in these patients and tends to mirror those with de novo stage III disease.[3,8,13] The outcome for patients receiving palliative therapy was poor, with a median survival of 9.8 months. Patients eligible for curative-intent therapies at recurrence should pursue aggressive treatment.

There were a variety of modalities used for curative-intent treatment of the relapsed disease, as seen in other retrospective studies.[6,14–22] The chosen treatment modalities are influenced by the initial treatment modality used in addition to other patient and disease characteristics. There was no clear difference in outcomes in our study comparing surgical intervention, SRS, and conventional RT greater than or equal to 60 Gy. Patients receiving 50 to 59 Gy of radiotherapy did seem to have poorer results compared with other modalities. Guidelines generally recommend a dose of 60 to 70 Gy for locally advanced disease[9,23]; however, hypofractionated regimens at lower total doses may provide a similar equieffective dose delivered in two fractions to 60 Gy. In our study, over half of the patients receiving 50 to 59 Gy were given a regimen of 55 Gy/20 fractions, corresponding to an equieffective dose delivered in two fractions of 58.2 Gy. The poorer outcomes with 50 to 59 Gy seen in this population may be owing, in part, to the low use of concurrent chemotherapy, and also selection bias, with less-fit patients being chosen for a shorter treatment course.

Although chemoradiation therapy is considered the preferred modality over radiation alone[9,23] for locoregional disease, only 41% of patients receiving curative RT in our study also received concurrent or sequential

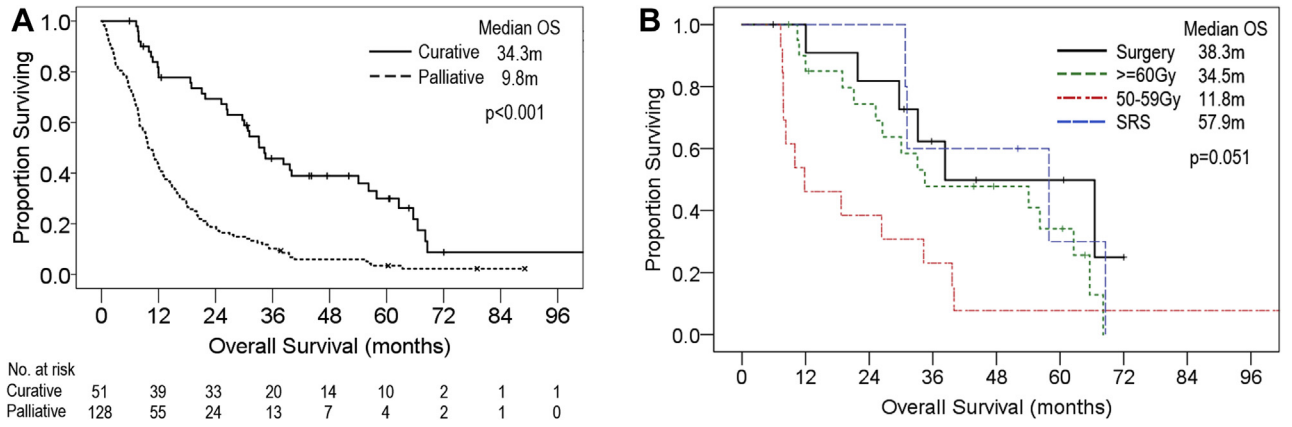

Figure 3. (*A*) Kaplan-Meier curve for OS from the date of diagnosis of recurrent disease (n = 179). (*B*) Kaplan-Meier survival curve for OS of the curative-intent group comparing radiotherapy and surgical treatments (n = 51). OS, overall survival; SRS, stereotactic radiosurgery.

Table 3. UVA and MVA Model of Factors Associated With OS

Characteristic	UVA HR[a]	95% CI	MVA HR[a]	95% CI
Cohort				
Curative	Ref		Ref	
Palliative	3.02	2.07-4.40	2.31	1.53-3.51
Type of recurrence				
Local	Ref		Ref	
Regional	1.07	0.73-1.57	1.03	0.69-1.52
Both	1.71	1.18-2.49	1.52	1.04-2.25
Age at recurrence, y				
With each year of increasing age	1.007	0.99-1.02	—	—
Sex				
Female	Ref		—	—
Male	1.18	0.86-1.61		
Histology				
Adenocarcinoma	Ref		—	—
Squamous	1.82	1.28-2.60		
NOS/other	1.42	0.92-2.18		
Stage at initial diagnosis				
I	Ref		Ref	
II	1.05	0.68-1.63	1.00	0.64-1.58
III	2.02	1.39-2.93	1.76	1.17-2.65
Smoking status				
Never	Ref		—	—
Former	1.91	1.05-3.46		
Current	2.30	1.28-4.16		
ECOG at recurrence				
0-1	Ref		Ref	
≥2	3.22	2.27-4.57	3.29	2.27-4.77

Notes: Never-smokers were defined as those who had less than 100 cigarettes over lifespan; former smokers were defined as those who quit greater than 1 year ago; current smokers were defined as actively smoking or quit less than 1 year ago.

[a]HR greater than 1.0 indicates increased risk of death.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MVA, multivariate analysis; NOS, not otherwise specified; OS, overall survival; Ref, referent; UVA, univariate analysis.

chemotherapy. Previous retrospective studies have also indicated that a significant proportion of patients are treated with RT alone.[3,7,10,11,13,24] This may be because of the lack of strong prospective evidence to support the use of chemoradiation in retreatment and patient factors that may make them ineligible for chemotherapy treatment. The patterns of practice may evolve with the incorporation of consolidative durvalumab after chemoradiotherapy as the standard of care.[25,26]

There are varied reports on the proportion of patients with locoregionally recurrent NSCLC who are eligible for salvage therapy with curative intent. Among patients treated initially with SRS for early stage disease, curative-intent salvage rates range from 24% to 70%.[3,5,13,20] There is less information available for patients who receive conventional radiotherapy, but one study suggested that a very low proportion of patients (4%) receive curative-intent therapy for isolated locoregional relapse.[27] Our study found similar results, with only 12% of patients treated with RT being eligible for curative-intent therapy at relapse.

The most common reasons for receiving noncurative therapy at relapse were nonmodifiable factors. Over half of the patients were treated with palliative therapy owing to the use of previous high-dose RT, and the resulting inability to treat with further curative doses of radiation. Most of these patients (80%) had stage III disease at initial diagnosis, requiring large treatment volumes using three-dimensional conformal radiotherapy or intensity-modulated radiotherapy. Regardless of the initial curative treatment technique and the availability of precision radiotherapy at the time of recurrence, it is often not possible to redeliver a curative radiation dose to the same volume while respecting normal tissue tolerances and avoiding potentially fatal complications including pneumonitis and tracheoesophageal fistula. Patients with stage III disease at initial diagnosis had inferior survival in our multivariate model, owing, in part, to this limitation on treatment options at recurrence. Now that immunotherapy with durvalumab has exhibited significant improvements in both disease-free and OS in the population of patients with

stage III NSCLC,[25,26] there should be a decrease in the overall proportion of this difficult-to-treat population.

Approximately one-fifth of patients were not eligible for curative therapy owing to the distribution of their disease. The guidelines suggest intermittent surveillance with chest computed tomography scans for several years after curative-intent treatment of NSCLC[9] despite a lack of prospective evidence to support this practice.[28] Previous studies have revealed that patients with asymptomatic recurrence have longer survival than those with symptomatic recurrence.[29–31] Although this could partially be attributed to lead-time bias, the survival difference persists even when measured from the date of initial curative therapy.[30] In addition, patients with asymptomatic recurrence have been reported to have an increased chance of receiving curative therapy at relapse.[31] Overall, our findings, in addition to the current evidence, support the use of surveillance imaging as there may be a population of patients whose disease would be amenable to salvage therapy if only detected earlier.

Palliative systemic therapy was given to less than half of the patients, consistent with other population-based studies of patients with metastatic disease.[32,33] With the growing role of personalized medicine with immunotherapy and targeted therapy in NSCLC,[34–37] systemic therapy uptake may improve over time as treatments become more effective and less toxic. Biomarker testing at BC Cancer became available in 2010 for EGFR, in 2014 for ALK, and in 2017 for programmed death-ligand 1. Low rates of testing in our population relate to both the time frame of the study and the lack of impact on therapy for patients treated with curative intent at relapse. More than half of the patients did not have a repeat biopsy at relapse, which may have impacted systemic therapy options. The tissue available from the original diagnosis may be sufficient for molecular testing; however, there is some suggestion that programmed death-ligand 1 expression may change over time or in the setting of previous treatment,[38–40] so the proportion of patients receiving pathologic confirmation at relapse may increase in the current era.

Our study is limited by its retrospective nature. Moreover, patients receiving curative therapy were more likely to have intensive staging investigations at relapse, with a much higher rate of PET scan use and the pursuit of pathologic confirmation of recurrence. This may bias the group receiving palliative therapy to poorer outcomes, as there may be presence of occult metastatic disease. However, in the sensitivity analysis, there was still a significant difference in OS between patients treated with curative versus palliative intent when the analysis was restricted only to patients with PET scan use or pathologic confirmation of recurrence. The time period included in this study precedes the widespread use of SRS for the initial treatment of inoperable early stage NSCLC. The use of SRS versus standard or hypofractionated regimens may change both patterns of recurrence and the proportion of patients eligible for curative-intent therapy at relapse.[3,5,13,20,27] There was no biomarker testing available for most patients; however, this would not be expected to change the treatment options for patients treated with curative intent. The strength of this study lies in the fact it contains a large population-based sample with robust survival data, which adds to the evidence base in an area in which no prospective evidence exists to guide treatment choices.

In conclusion, our retrospective study found that curative-intent treatment of local and regional relapses of NSCLC is associated with reasonable long-term survival, similar to de novo stage III disease. Unfortunately, most patients are not eligible for curative-intent treatment. Improving outcomes in this population is more difficult and may include more effective treatments at initial diagnosis, earlier detection of recurrence, and better systemic therapy after relapse.

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