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Scientific Article

Synchronous Oligometastatic Non-small Cell Lung Cancer Managed With Curative-Intent Chemoradiation Therapy: Long-term Outcomes From a Single Institution

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Abstract

Purpose: We examined long-term clinical outcomes among patients with synchronous oligometastatic non-small cell lung cancer (NSCLC) treated at our institution with definitive thoracic chemoradiation therapy (CRT) and local therapy to all oligometastatic lesions.

Methods and Materials: A retrospective review identified 38 patients with synchronous oligometastatic NSCLC ($\leq$3 metastatic lesions) who were treated with definitive CRT to the primary tumor and regional lymph nodes between 1999 and 2017 at our institution. Of the 38 patients, 27 patients (71%) received induction chemotherapy, all of whom responded or stabilized with initial systemic therapy before consideration of CRT. Most patients received chemotherapy concurrently with radiation therapy (n = 32; 84%) and local therapy to the metastatic disease site(s) (n = 34; 89%). We assessed patterns of progression or failure, overall survival (OS), progression-free survival (PFS), and toxicities.

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Results: The median follow-up duration was 54.9 months. Most patients (84%) presented with N2 to N3 disease. The brain or central nervous system was the most common site of disease progression and occurred in 16 of 28 patients (57%) experiencing any progression and 10 of 16 patients (63%) who initially presented with brain oligometastases. Median OS was 21.1 months (95% confidence interval [CI], 15.6-49.0 months), and median PFS 9.7 months (95% CI, 8.2-14.4 months). The 1-, 2-, and 4-year OS rates were 75.7%, 45.0%, and 33.7%, respectively. On multivariate analysis, both locoregional progression (hazard ratio: 5.8; 95% CI, 2.2-15.0; $P = .0003$) and distant progression (hazard ratio: 6.0; 95% CI, 2.3-15.4; $P = .0002$), when treated as time-dependent covariates, were associated with inferior OS. Grade $\geq$3 esophagitis occurred in 9% and grade $\geq$3 pneumonitis in 5% of patients with evaluable data.

Conclusions: Patients with synchronous oligometastatic NSCLC and a high regional nodal burden treated with definitive thoracic CRT experienced favorable survival outcomes and low toxicity. At our institution, treating oligometastatic disease with CRT after systemic therapy is incorporated into the treatment plan from the onset of therapy, and we monitor the neuraxis closely for progression during and after treatment. Future research should focus on novel treatment combinations, such as immunotherapy or targeted systemic therapy as appropriate to further improve tumor control and survival.

Introduction

Approximately half of all patients with non-small cell lung cancer (NSCLC) present with stage IV disease, which carries a historical median overall survival (OS) of 8 to 11 months and median progression-free survival (PFS) of 3 to 5 months after chemotherapy alone.[1-3] Traditionally, stage IV disease was considered to portend a uniformly poor prognosis. However, accumulating evidence suggests that carefully selected patients with a limited number of metastases (ie, oligometastases) may benefit from curative-intent therapy to the primary tumor and metastatic sites.[4-7]

Ashforth et al conducted a meta-analysis of primarily retrospective series, including 757 patients with NSCLC and 1 to 5 oligometastases who received ablative treatments to all disease sites.[8] Median OS was 26 months but was considerably reduced for patients with synchronous metastases and a higher nodal burden. In this meta-analysis, most patients (83.9%) received surgical resection to the primary tumor; the remainder received definitive radiation therapy (RT). Only 17.7% of patients received chemotherapy as part of primary lung cancer treatment.

More recently, Gomez et al conducted a multicenter randomized phase 2 trial with patients from 3 North American institutions who had stage IV NSCLC, $\leq$3 metastatic disease lesions, and no progression after $\geq$3 months of standard, first-line systemic therapy. Patients randomized to receive local consolidative therapy (LCT; n = 25), defined as radiation or surgery to all active disease sites, experienced superior PFS and OS compared with those randomized to receive maintenance therapy (systemic therapy) or observation (n = 24; median PFS: 14.2 vs 4.4 months; $P = .014$; median OS: 41.2 vs 17 months; $P = .017$).[4,9] Maintenance therapy was allowed at the discretion of the treating physician in the LCT arm.

A patterns-of-failure analysis by the University of Colorado found that patients with advanced NSCLC who were treated with first-line systemic therapy were more likely to fail at a lesion site known before treatment than at a new site.[10] This failure pattern further suggests the importance of aggressive local therapy for oligometastatic NSCLC.

We previously reported on the favorable outcomes for 9 patients with synchronous oligometastatic NSCLC who were given curative-intent chemoradiation therapy (CRT) to the primary tumor, regional mediastinal lymph nodes, and oligometastases at our institution.[11] We now report on the long-term outcomes in an expanded cohort (n = 38) with a more detailed analysis of patterns of progression or failure, OS, PFS, and toxicities.

Methods and Materials

Patient selection

After obtaining institutional review board approval, we conducted a retrospective review of clinical records to identify patients with stage IV NSCLC who were considered for thoracic RT between July 1999 to June 2017. The criteria for inclusion were as follows: (1) synchronous oligometastatic (M1) disease ($\leq$3 total metastatic lesion sites; N1-N3 lymph nodes were not counted as metastatic lesions); (2) histologically confirmed NSCLC treated with curative-intent CRT to the primary tumor and regional

lymph nodes; and (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

We identified 38 patients who met the inclusion criteria for this review. Patients underwent a complete history and physical examination, routine laboratory tests including complete blood count and chemistry panel, a computed tomography (CT) scan of the chest with contrast, and brain magnetic resonance imaging. All except 1 patient also received a staging positron emission tomography scan.

Treatment

Patients were reviewed in a multidisciplinary setting at thoracic tumor conferences consisting of surgical, medical, and radiation oncology as well as pathology, radiology, and pulmonary medicine physicians. The multidisciplinary team recommended treatment decisions based on factors such as performance status, location of the metastatic lesion(s), symptoms, and physician consensus. Patients were typically offered 2 to 6 cycles of induction chemotherapy, except for patients with brain metastases who had these lesions managed first. After induction chemotherapy, if the disease responded or stabilized (ie, no new or worsening lesions), patients received definitive, concurrent CRT to the primary tumor and regional mediastinal lymph nodes and usually RT to the oligometastatic site(s). Some patients with urgent respiratory symptoms received upfront CRT (with concurrent chemotherapy, if possible) to the primary tumor and regional lymph nodes.

Induction chemotherapy usually consisted of intravenous infusion of a carboplatin-based doublet, most commonly carboplatin (area under the curve = 6 per week) and paclitaxel (200 mg/m^2 per week) given every 3 weeks for 2 cycles. Concurrent chemotherapy during RT typically consisted of either carboplatin (area under the curve = 2 per week) and paclitaxel (45 mg/m^2 per week), or cisplatin (50 mg/m^2 on days 1, 8, 29, and 36) and etoposide (50 mg/m^2 on days 1-5 and 29-33).

Patients received conventionally fractionated RT (goal of $\geq$50 Gy in 1.8 or 2 Gy per fraction) with 3-dimensional conformal RT, intensity modulated RT, a mix of 3-dimensional conformal RT and intensity modulated RT, or proton therapy to the primary tumor and regional lymph nodes, except for 1 patient with T1N0 disease who received stereotactic body RT (SBRT; 41.25 Gy in 5 fractions).

Follow-up

Patients typically followed up with the treating oncologists every 1 to 3 months for the first year after CRT, every 3 to 6 months for the following 2 years, and every 6 to 12 months thereafter, or more often as clinically indicated. Patients received follow-up CT scans regularly after treatment, coordinated with the timing of follow-up appointments, and were managed with additional treatment as necessary.

Evaluation of tumor progression and toxicity

We reviewed patient follow-up notes and imaging to score sites of progression as locoregional (including primary tumor and regional lymph nodes) or distant (all other sites). We further classified each progression as occurring at a known lesion site (ie, present before treatment), new lesion site, or both. We considered locoregional and distant progression separately (ie, a patient who experienced locoregional progression could later experience distant progression, or vice versa), but repeated our analysis to consider only the first site of progression for a patterns-of-failure analysis.

Treatment-related toxicity data were available for 34 of 38 patients (89%). We used the Common Terminology Criteria for Adverse Events, version 4.03, to assess grade $\geq$3 esophagitis and pneumonitis among these patients.

Statistical analysis

We assessed OS and PFS using the Kaplan-Meier method. We measured OS from the start of treatment to the time of death, censored at the time of the last known follow-up visit. We measured PFS from the start of treatment to the time of either disease progression or death, censored at the time of the last known follow-up appointment or CT scan. We assessed associations between covariates and OS through univariate and multivariate Cox regression. Covariates included baseline patient characteristics (age, sex, ECOG performance status [1-2 vs 0], weight loss before diagnosis [>5% vs $\leq$5% of baseline body weight], histology, T stage [T3-4 vs all else], N stage [N3 vs all else], response to induction chemotherapy, number of oligometastatic lesion sites [1 vs all else], oligometastatic sites [brain vs all else and bone vs all else], and disease progression [locoregional and distant]). We treated locoregional and distant progression as time-dependent covariates for the regression analysis. All hypothesis tests were 2-sided. We considered $P < .05$ as statistically significant and performed the analyses with SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Table 1 describes the baseline patient characteristics and treatment to the primary tumor and regional lymph nodes. The median age was 64 years (range, 24-82 years). The majority of patients were women (n = 20; 53%) and presented with weight loss $\leq$5% of baseline (n = 27; 71%). Regional lymph node spread was relatively extensive, as 17 patients (45%) had N2 disease and 15

Table 1 Patient characteristics and treatment details to primary tumor and regional nodes

Characteristic	n (%)
Age (years)	
Median	64
Range	24-82
Sex	
Male	18 (47)
Female	20 (53)
Eastern Cooperative Oncology Group performance status score	
0	17 (45)
1	16 (42)
2	5 (13)
Weight loss	
Minimal (≤5% of baseline body weight)	27 (71)
Significant (>5%)	11 (29)
Histology	
Adenocarcinoma	26 (68)
Squamous cell carcinoma	5 (13)
Poorly differentiated carcinoma	7 (18)
T stage	
x	2 (5)
1	9 (24)
2	8 (21)
3	7 (18)
4	12 (32)
N stage	
x	2 (5)
0	2 (5)
1	2 (5)
2	17 (45)
3	15 (39)
Prescribed radiation dose (Gy)	
Median	60
Interquartile range	60-64
Range	41.25-72
Induction chemotherapy	
Yes	27 (71)
Carboplatin/paclitaxel	15
Cisplatin/docetaxel	3
Carboplatin/paclitaxel/bevacizumab	3
Cisplatin/paclitaxel	2
Carboplatin/paclitaxel/gemcitabine	2
Carboplatin/pemetrexed	1
Cisplatin/bevacizumab	1
No	11 (29)
Response to induction chemotherapy*	
Partial response	12 (44)
Stable disease	15 (56)
Concurrent chemotherapy	
Yes	32 (84)
Carboplatin/paclitaxel	21
Cisplatin/etoposide	5
Carboplatin	3
Carboplatin/pemetrexed	2
Carboplatin/paclitaxel/bevacizumab	1
No	6 (16)
Consolidation chemotherapy	
Yes	12 (32)
Carboplatin	2
Carboplatin/paclitaxel	2
Carboplatin/pemetrexed	2
Pemetrexed	3
Gemictabine/docetaxel	1
Docetaxel	1
Bevacizumab	1
No	26 (68)

* Based on response evaluation criteria in solid tumors version 1.1.

patients (39%) had N3 disease. Twenty-six patients (68%) presented with adenocarcinoma, 7 patients (18%) with poorly differentiated carcinoma, and 5 patients (13%) with squamous cell carcinoma.

The median prescribed RT dose was 60 Gy (interquartile range, 60-64 Gy) to the primary tumor and regional lymph nodes. Most patients received induction chemotherapy (n = 27; 71%) and chemotherapy concurrently with RT (n = 32, 84%). Of the 27 patients who received induction chemotherapy, 14, 3, 8, and 2 patients received 2, 3, 4, and 6 cycles, respectively. In addition, 12 of 27 patients (44%) achieved a partial response, and 15 of 27 patients (56%) had stable disease after induction chemotherapy. Twelve patients (32%) received consolidation chemotherapy, of which 6 patients had previously received induction chemotherapy.

Table 2 details oligometastatic sites at the time of presentation and treatment. The most common metastatic site was the brain (n = 18; 47%), which was most often treated with stereotactic radiosurgery (SRS) alone (n = 9). Only 1 patient had metastases to >1 extrathoracic organ (brain and bone). Twenty-seven patients (71%) presented with a single metastatic lesion site. Most patients (n = 33; 87%) were managed with RT to the oligometastatic sites, and of the other 5 patients, 1 patient received radiofrequency ablation for a liver metastasis and 4 patients did not receive local therapy to the oligometastasis because of a favorable response to induction chemotherapy.

Patterns of progression/failure

The median follow-up duration was 54.9 months (95% confidence interval [CI], 28.3 months to not reached). Table 3 details the crude patterns of progression. Twenty-eight patients (74%) experienced any disease progression, with locoregional progression occurring in 10 patients (26%) and distant progression in 24 patients (63%). The most common location of distant progression was the brain and central nervous system (CNS; n = 16), and of

Table 2 Oligometastatic sites at the time of presentation and treatment

Metastatic Site(s)	n (%)	Treatment
Brain	16 (42)	SRS (n = 9) 20 Gy/1 Fx (n = 8) 16 Gy/1 Fx (n = 1) Resection + postoperative SRS (n = 3) 20 Gy/1 Fx (n = 2) 35 Gy/5 Fx (n = 1) WBRT (n = 3) 30 Gy/10 Fx (n = 2) 37.5 Gy/15 Fx (n = 1) Resection + postoperative WBRT (34 Gy/14 Fx) (n = 1)
Bone	8 (21)	30 Gy/10 Fx (n = 2) 27 Gy/9 Fx (n = 1) 37.5 Gy/15 Fx (n = 1) 41.4 Gy/23 Fx (n = 1) 46 Gy/23 Fx (n = 1) 60 Gy/30 Fx (n = 1)
Lymph node	4 (11)	59.4 Gy/33 Fx (n = 2; axillary and cervical) 50.4 Gy/28 Fx (n = 1; axillary) 60 Gy/30 Fx (n = 1, subpectoral)
Adrenal gland	3 (8)	36 Gy/12 Fx (n = 1)
Pericardial fluid	2 (5)	46 Gy/23 Fx (n = 1) 66 Gy/33 Fx (n = 1)
Pleura	2 (5)	60 Gy/30 Fx (n = 1)
Liver	1 (3)	Radiofrequency ablation
Brain and pleura	1 (3)	Resection + postoperative SRS (20 Gy/1 Fx); 60 Gy/30 Fx
Brain and bone	1 (3)	Resection + postoperative SRS (20 Gy/1 Fx); 16 Gy/1 Fx

Abbreviations: Fx = fraction; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy.

these 16 patients, 10 patients (63%) had originally presented with brain oligometastases. Progression in the brain and CNS occurred in 10 of 16 patients (63%) with brain oligometastases at the time of presentation and in 6 of 22 patients (27%) without brain oligometastases at the time of presentation. None of the 22 patients without brain oligometastases at the time of presentation experienced disease progression in the oligometastatic organ or site, including the 4 patients who did not receive local therapy to the oligometastatic site.

Table 4 details patterns of failure (defined as first progression, including simultaneous sites of failures). Of the 28 patients who experienced disease progression, 4 patients (14%) failed at a known primary tumor, mediastinal lymph node or oligometastatic lesion site, 18 patients (64%) failed at a new lesion site, and 6 patients (21%) failed at both. Treatment after failure included chemotherapy alone (n = 7), SRS (n = 6), whole brain RT (WBRT) and chemotherapy (n = 3), WBRT alone (n = 2), immunotherapy (n = 2; nivolumab and nivolumab/ipilimumab), targeted systemic therapy (n = 1; erlotinib), SBRT to a lung lesion (n = 1), and definitive RT to an inguinal lymph node (n = 1). The remaining 5 patients received supportive care only (including palliative RT) because of a poor performance status at the time of disease recurrence.

Table 3 Patterns of progression

Site of progression	n (%)
Any progression	28 (74)
Locoregional	10 (26)
Distant*	24 (63)
Brain/central nervous system	16†
Contralateral lung	4
Bone	3
Kidney	1
Peritoneal carcinomatosis	1
Retroperitoneal lymph node	1
Inguinal lymph node	1
Paraspinal muscle	1

* Three patients experienced distant progression in at least 2 separate sites simultaneously.

† Two patients experienced leptomeningeal carcinomatosis.

Overall and progression-free survival

Death was documented in 28 patients (74%). Of the remaining 10 patients, 8 patients were still alive as of December 2018 and 2 patients were lost to follow up. Median OS was 21.1 months (95% CI, 15.6-49.0 months), with 1-, 2-, and 4-year OS rates of 75.7%, 45.0%, and 33.7%, respectively (Fig 1A). Median PFS was 9.7 months (95% CI, 8.2-14.4 months), with 1- and 2-year PFS rates of 40.7% and 21.1%, respectively (Fig 1B).

On univariate analysis, both locoregional progression (hazard ratio [HR]: 4.8; 95% CI, 1.9-12.0; $P = .0008$) and distant progression (HR: 5.3; 95% CI, 2.1-13.2; $P = .0004$), when treated as time-dependent covariates, were associated with inferior OS. Age, sex, ECOG performance status, weight loss before diagnosis, histology, T stage, N stage, response to induction chemotherapy, number of oligometastatic lesion sites, and oligometastatic sites were not significant predictors of OS ($P > .05$ for all). On multivariate analysis, locoregional progression (HR: 5.8; 95% CI, 2.2-15.0; $P = .0003$) and distant progression (HR: 6.0; 95% CI, 2.3-15.4; $P = .0002$) retained significance as predictors of worse OS.

Table 4 Patterns of failure (first progression) among 28 patients who experienced progression

Patient number	Initial oligometastatic site(s)	Site(s) of failure*	Known lesion site, new lesion site, or both†
1	Brain	Brain	Both
2	Brain	Brain	Both
3	Brain	Brain	New
4	Brain	Brain	New
5	Brain	Brain	New
6	Brain	Brain	New
7	Brain	Brain, contralateral lung, locoregional	Both
8	Brain	Leptomeningeal	New
9	Brain	Brain, bone, paraspinal muscle	New
10	Brain	Locoregional	Known
11	Brain	Contralateral lung	New
12	Brain	Bone	New
13	Brain, pleura	Brain, locoregional	Both
14	Bone	Locoregional	Known
15	Bone	Locoregional	Both
16	Bone	Retroperitoneal lymph node	New
17	Bone	Inguinal lymph node	New
18	Bone	Brain	New
19	Bone	Brain	New
20	Axillary lymph node	Contralateral lung	New
21	Axillary lymph node	Brain	New
22	Cervical lymph node	Brain	New
23	Adrenal	Locoregional	Known
24	Adrenal	Locoregional	Known
25	Pericardial fluid	Brain	New
26	Pericardial fluid	Leptomeningeal	New
27	Pleura	Contralateral lung, locoregional	Both
28	Liver	Bone, kidney	New

* Some patients experienced synchronous failures in multiple sites.

† Distinct metastases within 1 organ were counted as separate lesions.

Toxicity

Of the 34 patients evaluable for toxicity, 3 patients (9%) experienced grade ≥3 esophagitis and 2 patients (5%) experienced grade ≥3 pneumonitis. No grade 4 or 5 treatment-related toxicities of any type occurred among these 34 patients.

Discussion

We observed a favorable OS (median: 21.1 months; 1-year rate: 75.7%) and PFS (median: 9.7 months; 1-year rate: 40.7%), and low toxicity rates among patients with synchronous oligometastatic NSCLC treated with curative-intent CRT (concurrent in 84%) to the primary tumor and regional lymph nodes and local therapy to the metastatic sites (in 89%). The median OS and PFS appear similar to outcome data for stage IIIB NSCLC treated with CRT.[12,13] These outcomes are perhaps more notable in light of the high nodal burden (N2-N3 disease in 84%) and inclusion of only patients with synchronous metastases, the combination of which was previously shown to associate with inferior OS within the oligometastatic patient population (1-year OS: 48.9%-53.6% for N1-N2 disease).[8]

Several prospective phase 2 trials, both single-arm and randomized, demonstrated favorable outcomes for patients with oligometastatic NSCLC treated with curative intent to the primary tumor and metastatic lesions (Table 5).[4,5,14-16] In these studies, median OS ranged from 13.5 to 41.2 months, and median PFS from 9.7 to 14.2 months. The nodal burden in these studies was relatively lower (N2-N3 disease in 40%-59%) than in our cohort. In addition, inclusion criteria and treatment schemes varied, and patients typically received definitive RT to the primary tumor without concurrent chemotherapy.

In contrast with several of these trials, for patients with significant mediastinal disease, we typically employed conventionally fractionated RT (approximately 60-66 Gy in 30-33 fractions) with chemotherapy instead of hypofractionated RT (approximately 45-60 Gy in 10-15 fractions) without concurrent chemotherapy. The former theoretically allows for concurrent treatment of micrometastatic disease in patients with early stage IV disease, but the latter may allow for higher biological effective doses and decreases the overall treatment time, thereby potentially leading to less time off full-dose systemic therapy.[17] Similarly, the majority of our patients did not receive SBRT for their extracranial metastases, which reflects the earlier period of treatment.

In our cohort of patients with synchronous oligometastatic disease from NSCLC, a significant finding was that locoregional progression was associated with worse OS even after accounting for distant progression, which suggests that locoregional control is important in this patient population. Xanthopoulos et al also demonstrated that local tumor control correlated with OS among 29 patients with oligometastatic NSCLC treated with definitive thoracic RT (and concurrent chemotherapy in 55%).[18] Traditionally, patients with stage IV disease received palliative RT to the thorax with the thought that distant disease control was a stronger contributor to OS.

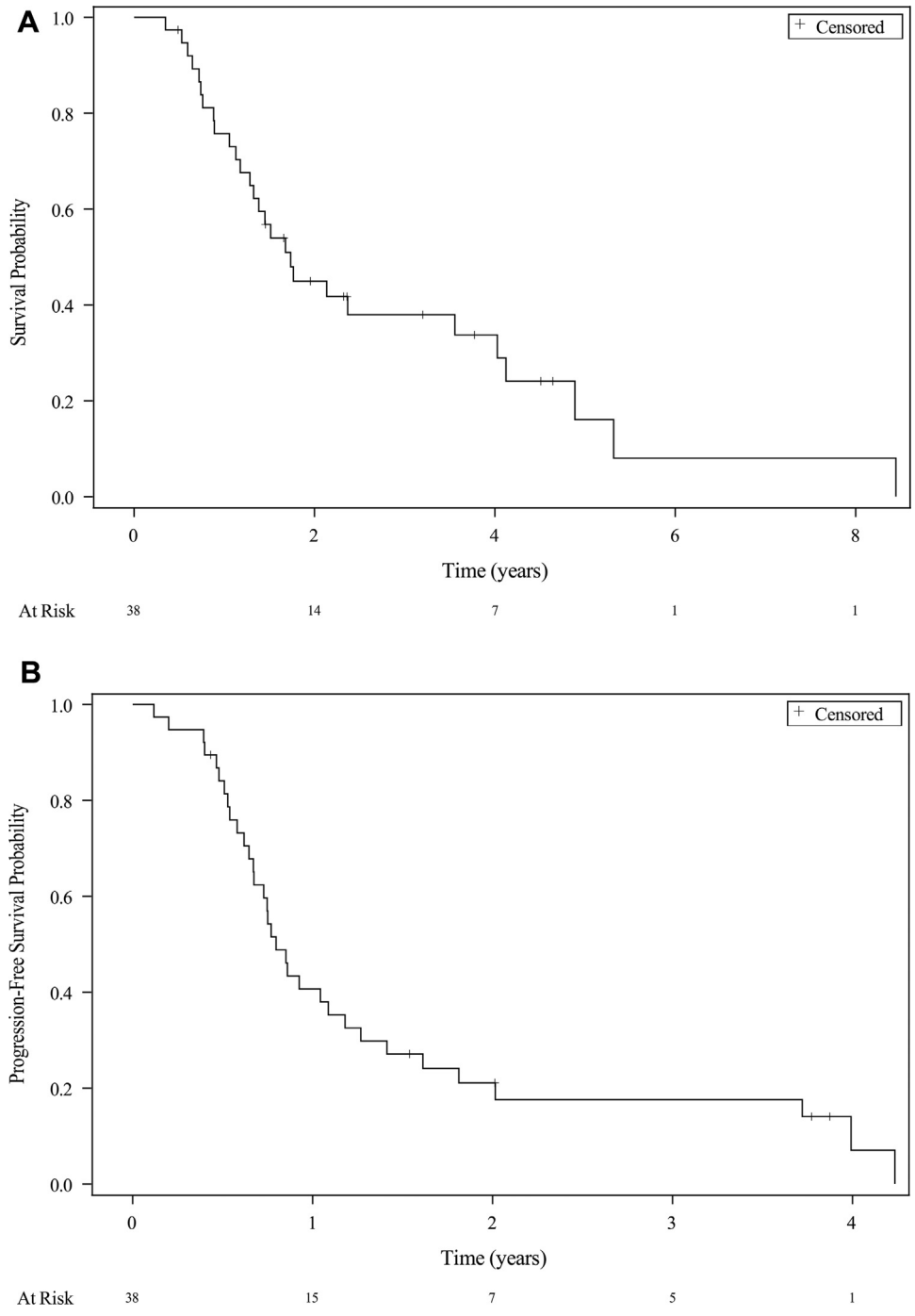

Figure 1 Kaplan-Meier curves for (A) overall survival and (B) progression-free survival of the cohort.

Locoregional control is possibly a functional marker of the effectiveness of dual-modality CRT. However, these findings are hypothesis-generating, given the limitations in correlating disease progression with OS, the fact that 5 of 10 patients with locoregional progression experienced simultaneous or prior distant progression, and the possibility for unmeasured confounders.

Failure in the brain and CNS accounted for 16 of 28 failures (57%) and was relatively common even among patients without brain oligometastases at the time of initial presentation. By contrast, other oligometastatic sites were well controlled after hypofractionated RT. Therefore, patients with oligometastatic disease should probably undergo close surveillance of the neuraxis after initial treatment. Moreover, of the 16 patients who presented with brain oligometastases, 12 patients (75%) received local therapy that consisted of SRS with or without resection. Of these 12 patients, 7 patients (58%)

Table 5 Phase 2 trials testing definitive thoracic radiation therapy for stage IV oligometastatic non-small cell lung cancer

Study and year	Treatment for primary tumor and regional nodes	n	% Synchronous	N stage	Median OS (months)	Median PFS (months)
De Ruysscher et al, 2012[14]	Concurrent CRT (54%), sequential CRT (39%), or RT alone (5%)	39	100	N2-N3: 59%	13.5	12.1
Collen et al, 2014[15]	Hypofractionated RT ± induction chemo	26	73	N2-N3: 52%	23	11.2
Gomez et al, 2016 and 2018[4,9]*	Arm 1: First-line systemic therapy followed by LCT (intermediate/standard fractionated RT [56%], SBRT [20%] or surgery [12%]) ± maintenance therapy	25	96	N2-N3: 52%	41.2	14.2
	Arm 2: First-line systemic therapy followed by maintenance therapy or observation	24	92	N2-N3: 54%	17	4.4
Iyengar et al, 2018[5]*	Arm 1: Induction chemo + SBRT/ hypofractionated RT + maintenance chemo	14	NR	NR	Not reached	9.7
	Arm 2: Induction chemo + maintenance chemo	15	NR	NR	Not reached	3.5
Petty et al, 2018[16]*	Induction chemo + consolidative RT (conventionally fractionated or SBRT)	27	NR	N2-N3: 40%	28.4	11.2

Abbreviations: chemo = chemotherapy; CRT = chemoradiation therapy; LCT = local consolidative therapy; NR = not reported; OS = overall survival; PFS = progression-free survival; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

* Only included patients who did not progress after first-line systemic therapy or induction chemotherapy.

subsequently failed in the brain and CNS, each at a site remote from the original SRS field. Similarly, De Ruysscher et al found that 9 of 17 patients (53%) who received SRS for brain oligometastases from a lung primary had a cerebral recurrence at a site distinct from the original SRS field.[14] In both studies, CNS recurrences were likely present as micrometastases at the time of original treatment. Because randomized evidence suggests that WBRT after SRS improves intracranial tumor control (albeit with more cognitive deterioration and no benefit in OS), WBRT could warrant further investigation among those with oligometastatic NSCLC.[19-21] We recommend routine scheduled imaging of the brain as part of restaging studies along with imaging for other visceral disease sites.

Among patients who received induction chemotherapy in our cohort (n = 27), patients with stable disease did not appear to fare significantly worse than the partial responders with respect to OS (HR: 1.1; $P = .79$) or PFS (HR: 1.6; $P = .28$). Gomez et al were also unable to demonstrate a difference in PFS for patients with stable disease after first-line systemic therapy versus responders (HR: 0.77; $P = .48$).[4] Additional studies with larger sample sizes are needed to clarify whether response to initial systemic therapy is prognostic after aggressive local treatment of oligometastatic disease. Nevertheless, we recommend initial systemic therapy for patients with oligometastatic disease because we believe response and stabilization after initial systemic therapy may select for a patient population that is more likely to respond to definitive CRT. At our institution, some patients with urgent respiratory symptoms are offered upfront CRT, and any disease in the brain is addressed first.

The advent of immunotherapy represents a paradigm shift in the treatment of stage III and IV NSCLC. The PACIFIC trial demonstrated a 10.7% improvement in the 2-year OS rate for patients with stage III NSCLC treated with consolidation durvalumab.[22] For patients with newly diagnosed stage IV NSCLC, the KEYNOTE-189 and KEYNOTE-042 trials demonstrated the superiority of pembrolizumab plus chemotherapy versus chemotherapy regardless of programmed death ligand-1 (PD-L1) tumor proportion score (TPS) and of pembrolizumab versus chemotherapy in the setting of PD-L1 TPS $\geq$1%, respectively.[23,24] Patients with oligometastatic NSCLC likely represent a group in between stage III and stage IV disease, reflected in the new distinction between stage IVA and IVB in the American Joint Commission on Cancer 8th edition criteria.[25]

Given that both locoregional and distant control predicted for improved OS in our cohort of patients, coupled

with the low toxicity we observed after CRT, our study underscores the importance of ongoing and future work to identify how best to integrate immunotherapy or targeted systemic therapy for oligometastatic NSCLC. Notably, the NRG LU002 trial (NCT03137771), an ongoing randomized phase 2/3 trial evaluating maintenance chemotherapy with or without SBRT or hypofractionated RT in patients with oligometastatic NSCLC who do not progress after first-line systemic therapy, underwent an amendment to allow for immunotherapy. Several recently launched trials aim to extend the paradigm of LCT to the setting of polymetastatic NSCLC (>3 metastatic lesions allowed), including the phase 3 LONESTAR trial (NCT03391869; LCT after nivolumab/ipilimumab) and phase 2 NORTHSTAR trial (NCT03410043; LCT after osimertinib in patients with epidermal growth factor receptor [EGFR] mutations).

Our study retains several limitations, including a retrospective design, small sample size, and somewhat heterogeneous population. However, we found limited data on the routine use of concurrent CRT for patients with oligometastatic NSCLC,[14,18,26] as well as for patients with extensive mediastinal lymph node involvement, which our study addresses. The median follow-up duration of 54.9 months represents a relative strength. The study is also limited by a reasonable possibility of selection bias. Although we were unable to compare patients treated with definitive CRT to those treated with chemotherapy alone, multiple studies suggest a benefit for including definitive local therapy. The randomized phase 2 trials by Gomez et al and Iyengar et al showed significant benefits in PFS with LCT and SBRT/hypofractionated RT, respectively, although only 49 and 29 patients, respectively, were randomized.[4,5] Retrospective studies used propensity-score matching to suggest improvements in survival with local therapy,[27,28] and a recent meta-analysis of retrospective studies provides further support for the benefits of aggressive thoracic therapy (either surgery or RT) for patients with synchronous oligometastatic NSCLC.[29] An additional limitation is that the EGFR mutational status was unknown for most patients in our study. Emerging retrospective data suggest a benefit to LCT after first-line EGFR tyrosine kinase inhibitor therapy for this population.[30,31]

Conclusions

We observed favorable OS, PFS, and toxicity rates among patients with synchronous oligometastatic NSCLC and a high mediastinal lymph node burden treated with definitive thoracic CRT, rivaling those observed among patients with stage III disease, and similar to those from other oligometastatic studies. Among recipients of induction chemotherapy, CRT was only considered for patients who responded or stabilized after the initial systemic therapy. Notably, locoregional progression was associated with worse OS. At our institution, treating oligometastatic disease with CRT is incorporated into the treatment plan from the onset of therapy instead of after many rounds of initial systemic therapy, and we monitor the neuraxis closely for progression during and after treatment. This highly selected patient population may further benefit from the integration of immunotherapy or targeted systemic therapy for which further prospective studies appear warranted.

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