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ORIGINAL RESEARCH REPORT

Multimodality therapy improves survival in intramedullary spinal cord metastasis of lung primary

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Abstract
Background: Most metastatic spinal cord lesions are located either in the intradural, extramedullary, or in the epidural compartments. Intramedullary spinal cord metastasis (ISCM) is a rare central nervous system spread of cancer. The aim of this report was to evaluate ISCM in the published literature.
Methods: A literature review of PubMed from 1960 to 2016 was undertaken for the publications having demographic, clinical, histological, and outcome data.
Results: A total of 59 relevant papers were identified, showing 128 cases of intramedullary metastasis from lung cancer. The incidence of lung cancer as the primary malignancy with intramedullary metastasis was 56%. The median time from diagnosis of primary to intramedullary metastasis was 6 months. Survival improved with multimodality therapy compared to monotherapy (4 months vs. 6.3 months) (hazard ratio = 0.501; 95% confidence interval, 0.293–0.857).

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Conclusion: Lung cancer is the predominant cause of intramedullary involvement of the spinal cord. Overall prognosis is poor, although a multimodality approach was associated with improved survival.

Introduction

Metastatic spread of cancer to the central nervous system is common and usually causes death. Spinal metastatic disease frequently manifests as spinal cord compression, owing to the extension of growth from the vertebral column with epidural lesions, or leptomeningeal involvement with intradural, extramedullary lesions. A small fraction, however, can metastasize to the intramedullary portion of the spinal cord (ISCM) and have different clinical presentations and outcomes.

Little is known of this rare condition, but primary lung cancer is thought to be the most common malignancy to cause ISCM. In the limited literature, ISCM is believed to represent less than 5% of all spinal metastasis [1]. Spread of disease to ISCM is thought to be from direct tumor infiltration or by hematogenous spread of cancer cells. The ISCM retains the blood—brain barrier, which hinders the initial spread of metastatic disease, but also inhibits the infusion of chemotherapy along with regulatory mechanisms.

As patients are living longer and disease recurrence in the central nervous system is increasing, we sought to review the literature and analyze the clinical characteristics of ISCM.

Materials and methods

We charged three authors with reviewing Pubmed search engine using the keywords (intramedullary, metastasis, lung) independently. Results were then combined, and conflicts in interpretation were resolved by mutual discussions. The search covered articles in English literature with human subject matter from January 1960 through December 2015. Results were then reviewed to extract raw data including age, sex, presentation, time from cancer diagnosis, pathology of the lung cancer, site of spinal cord involvement, diagnostic method, cerebrospinal fluid cytology, and associated brain and/or leptomeningeal metastatic disease. The time from diagnosis of spinal metastases until death, loss of follow-up, or living at time of reporting were measured and converted to months using the following formula: 1 week = 0.23 month.

Kaplan—Meier curves and log-rank tests were used to evaluate the association between categorical variables and survival time. The univariate Cox model was used to obtain the estimated hazard ratio (HR) between two groups. SPSS version 22 (IBM Corp., Armonk, NY, USA) was used to perform statistical analysis.

Results

Out of the 133 articles returned by searching, 59 were relevant and involved lung cancer. These included 22 case series (Table 1) and 37 single case reports (Table 2), with the total number of intramedullary metastatic cases being 128. Lung cancer was the primary malignancy in 56% of the reported cases in the mixed series (Table 1).

Age and sex distributions were recorded for all the patients ($n = 128$) with the median age being 60 years. Men were reported with 3:1 distribution. The median time to diagnosis ($n = 91$) was 6 months (range, 0—49 months). Pathology of the lung primary was available for most of the cohort ($n = 123$), with small cell lung carcinoma (SCLC) being the primary pathology in 40.7% ($n = 50$) versus non-small cell lung carcinoma (NSCLC) with a distribution of 20.3% adenocarcinoma, and 6.3% squamous of the total reported cases. It does not appear that metastatic disease from SCLC resulted in significantly worse survival ($p = 0.27$).

Magnetic resonance imaging was the modality for diagnosis in 52% ($n = 39$), whereas computed tomography was used in 5.3% and positron emission tomography in 4%. Twenty-three patients (30.7%) were diagnosed *postmortem*.

Regions of disease were reported in 85.9% ($n = 110$). The cervical region was the most common area of intramedullary metastases with 34.5% of the available data revealing involvement. Thoracic and lumbar disease consisted of approximately two-thirds of cases. Multilevel involvement was reported in 25.5% ($n = 28$). There was no statistically significant overall survival difference when comparing one region of involvement versus multiregional ($p = 0.15$).

Interestingly, leptomeningeal disease was reported in 31.3% ($n = 40$) of the examined cases, but when cerebrospinal fluid was measured, cytology was positive in only 11.4% out of the 44 cases. There were 42 cases with concomitant brain metastasis, which was associated with comparable survival to the ones with negative brain metastasis with an HR of 1.01 (95% confidence interval, 0.56—1.84; $p = 0.956$).

Treatments used were reported in 79 of the cases. Most patients received steroids for symptomatic management. Multimodality treatment of spinal metastases included radiation, intrathecal and systemic chemotherapy, and/or surgery. A higher proportion received radiation (36.7%) and multimodality treatment (43%), as compared to surgery alone (17.7%). The multimodality group had significantly better survival outcome as compared to single form of therapy, with median survival of 6.3 months versus 4 months, respectively (Fig. 1; $p = 0.008$, HR = 0.50; 95% confidence interval, 0.29—0.86).

Discussion

We hereby collectively studied intramedullary spinal cord metastasis arising from a lung primary. Our review shows that the use of multimodality therapy with surgery,

Table 1 Case series of intramedullary spinal metastasis of lung primary.

Study	Total	Age (y)	Sex	Time since diagnosis (months)	Histology	Treatment	Survival (months)	Status
Benson [11]	3	59	m	12	NSCLC		0.69	Deceased
		58	m	2	NSCLC	Radiation	4	Deceased
		56	m	0	NSCLC		2	Deceased
Sherbourne et al. [12]	2	69	m	36	NSCLC		0.23	Deceased
		60	m		NSCLC		3	Deceased
Belmusto et al. [13]	5	40	m	6	SCLC	Surgery	2	Deceased
Edelson et al. [14]	9	76	m	0	NA	Radiation	0.46	Deceased
		40	m	10	SCLC	Radiation	2.07	Deceased
		49	m	6	SCLC	Radiation	0.23	Deceased
		43	f	0	NSCLC	Radiation	1.38	Deceased
Puljic et al. [15]	4	63	m	0	NA			
		64	m		NSCLC	Radiation		
Jellinger et al. [16]	7	69	f	0	SCLC		1.38	Deceased
		78	m	0	SCLC		2	Deceased
Moffie and Stefanko [17]	3	71	m	0	NSCLC			
Hashizume and Hirano [18]	5	50	m		SCLC			
		59	f		NSCLC			
		39	f		NSCLC			
		72	m		SCLC			
Murphy et al. [19]	4	58	f	10	SCLC	Radiation	1	Deceased
		54	f	11	SCLC	Radiation	9	Deceased
		45	m		SCLC	Radiation	10	Deceased
		62	m	0	SCLC	Radiation	7	Deceased
Costigan and Winkelman [20]	13	60	m		NSCLC		0.34	Deceased
		60	m		NSCLC		2	Deceased
		63	m		NSCLC		3	Deceased
		46	f		SCLC	Radiation		
		69	m		SCLC		7	Deceased
		63	f		NSCLC			
		42	m		SCLC			
		49	m		SCLC			
		66	m		NSCLC			
		56	m		NSCLC			
		36	m		NSCLC			
Grem et al. [21]	5	56	m	36	SCLC	Multimodality	13	Deceased
		54	f	10	SCLC	Radiation		
		45	m	9	SCLC	Radiation	4	Deceased
Findlay et al. [22]	2	74	m	0	NSCLC	Multimodality	3	Deceased
Tognetti et al. [23]	5	59	m	0	NSCLC	Radiation	7	Deceased
		41	m	0	SCLC	Surgery	2.5	Deceased
		61	m	8	NSCLC		1.47	Deceased
Connolly et al. [24]	3	35	f	0	NSCLC	Multimodality	6.5	Deceased
		62	m	0	NSCLC	Multimodality	11	Deceased
Sutter et al. [25]	3	54	m	0	NSCLC	Surgery	6	Deceased
		45	m	0	SCLC	Surgery	8	Deceased
Potti et al. [6]	7	62	m		NSCLC	Multimodality	4.6	Deceased
		62	m		NSCLC	Multimodality	6.3	Deceased
		69	f		NSCLC	Multimodality	1.3	Deceased
		61	m		NSCLC	Multimodality	23.5	Deceased
		64	m		NSCLC	Multimodality	16.6	Deceased
		68	f		NSCLC	Multimodality	9.3	Deceased
		62	m		NSCLC	Multimodality	10	Deceased

(*continued on next page*)

Table 1 (*continued*)

Study	Total	Age (y)	Sex	Time since diagnosis (months)	Histology	Treatment	Survival (months)	Status
Watanabe et al. [5]	7	79	m	0	SCLC			
		70	m	0	SCLC	Surgery	5	Deceased
		61	m	16	SCLC			
		53	m	0	NSCLC	Radiation	9	Deceased
		61	m	8	SCLC			
Lee et al. [26]	12	61	m	9.5	SCLC	Radiation	2	Deceased
		63	m	13.9	SCLC	Radiation	1	Deceased
		65	f	10.1	SCLC	Radiation	8.8	Deceased
		32	f	7.9	NSCLC	Radiation	0.8	Deceased
		77	m	0.2	NSCLC	Radiation	1	Deceased
		73	m	0	NSCLC		18.4	Deceased
Dam-Hieu et al. [9]	19	43	m	24	NSCLC	Surgery	2	Deceased
		68	m	12	NSCLC		0.11	Deceased
		50	m	11	SCLC	Multimodality	6	Deceased
		47	f	18	NSCLC	Multimodality	8	Deceased
		39	f	12	SCLC		4	Deceased
		66	m		NSCLC		1	Deceased
		57	m	3	NSCLC	Multimodality	4	Deceased
		56	f	12	SCLC	Multimodality	5	Deceased
		49	m	18	NA	Multimodality	2	Deceased
		66	m	6	NSCLC		0.46	Deceased
		55	m	24	NSCLC	Multimodality	11	Deceased
		68	f	24	SCLC	Multimodality	15	Deceased
		65	f	20	SCLC	Multimodality	4	Deceased
Hashii et al. [27]	18	49	m		NSCLC		1.84	Deceased
		55	m		NSCLC		5.98	Deceased
		57	m		NSCLC		2.07	Deceased
		64	f		NSCLC		3.91	Deceased
		65	m		NSCLC		0.92	Deceased
		76	m		NSCLC		4.6	Deceased
		67	m		SCLC		4.6	Deceased
		72	f		SCLC		6.44	Deceased
Sung et al. [1]	8	63	m	1	NA	Multimodality	4	Deceased
Payer et al. [28]	22	77	m	0	NSCLC	Surgery	3	Alive
		64	f	6	NSCLC	Multimodality	4	Alive
		34	f	49	NSCLC	Multimodality	6	Alive
		27	m	13	NSCLC	Multimodality	13	Alive
		60	m	0	NSCLC	Multimodality	3	Alive
		54	m	46	NSCLC	Surgery		

f = female; m = male; NA = not available; NSCLC = nonsmall cell lung carcinoma; SCLC = small cell lung carcinoma; y = year.

radiotherapy, and chemotherapy might improve the dismal survival associated with this disease.

Surveillance research from the American Cancer Society for 2016 demonstrates lung cancer to be the second leading cause of new cancer cases and is a leading cause of cancer mortality, being responsible for 27% of all cancer deaths. Intramedullary spinal cord metastatic disease is a rarely studied complication of primary lung cancer and represents less than 5% of total spinal cord metastasis. We do understand that direct tumor infiltration and hematogenous spread are the two most common methods of metastasis to the spinal cord, which are the proposed methods in ISCM also. Our goal was to review cases of ISCM in order to identify imaging and/or treatment approaches to impact and potentially improve clinical practice. We included reported case studies of intramedullary metastasis from 1960 to increase the reliability of information being extracted and capture modern approaches of management. The analysis showed comparable results to previous reports of lung cancer as being the most common source of metastasis [1,2]; however, this could also be related to selection bias given the exclusion of published paper with no lung cancer involvement.

Prior to the introduction of advanced imaging techniques and early detection of lung cancer in the 1980s, sensorimo-

Table 2 Case reports of intramedullary spinal metastasis from the lung.

Study	Age (y)	Sex	Time since diagnosis (months)	Histology	Treatment	Survival (months)	Status
Smith and Turner [29]	66	m	0	SCLC	Surgery	1.38	Deceased
Hirose et al. [30]	57	m	0	NSCLC		3	Deceased
Sebastian et al. [31]	51	m	0	SCLC	Multimodality	1.38	Deceased
Reddy et al. [32]	64	m	10	SCLC			
Weissman and Grossman [33]	48	m	6	SCLC	Multimodality	1	Deceased
Lazzarino et al. [34]	63	m	0	SCLC			
Koelman et al. [35]	54	f	24	NSCLC	Multimodality	13	Deceased
Aoki et al. [36]	75	m		NSCLC		1.6	Deceased
Jayasundera et al. [7]	59	m	11	NSCLC	Radiation		
Keung et al. [37]	39	f	9	NSCLC	Radiation	2.3	Deceased
Vindlacheruvu et al. [38]	54	f	0	SCLC	Multimodality	6	Deceased
Fujimoto et al. [39]	59	m	6	SCLC	Radiation	6	Deceased
Komori and Delbeke [8]	64	m	11	NSCLC			
Mortimer et al. [40]	69	m		NSCLC	Radiation	0.46	Alive
Reddy et al. [41]	80	m	30	NSCLC	Multimodality	2	Alive
Aryan et al. [42]	59	m	0	NSCLC		8	Alive
Kalayci et al. [43]	72	m	6	NSCLC	Surgery	8	Deceased
Guppy and Wagner [44]	54	m	0	NSCLC	Surgery	4	Deceased
Koutsis et al. [45]	60	m	10	SCLC	Radiation	1	Deceased
Nikolaou et al. [46]	47	f	3	SCLC	Chemotherapy	4	Deceased
Marquart et al. [4]	74	m	0	NSCLC	Multimodality	4.14	Deceased
Ashawesh et al. [47]	68	m	4	SCLC	Radiation		
Li et al. [48]	33	f	48	NSCLC	Multimodality	0.46	Alive
Soga et al. [49]	73	m		NSCLC		2	Deceased
Liu et al. [50]	44	m	36	NSCLC	Surgery	8	Deceased
Sari et al. [3]	50	f	0	SCLC			
Hata et al. [10]	35	m	8	NSCLC	Multimodality	84	Alive
Zhang et al. [51]	58	m	0	SCLC	Radiation	9	Deceased
Mavani et al. [52]	46	m	0	NSCLC	Multimodality	2	Alive
Gainor et al. [53]	31	m	30	NSCLC	Radiation	5	Alive
Nishioka et al. [54]	76	m	0	SCLC	Surgery	1.6	Deceased
Mori et al. [55]	67	m	12	NSCLC	Radiation	10	Deceased
Katsenos and Nikolopoulou [56]	74	m	0	SCLC	Multimodality	3	Deceased
Miura et al. [57]	59	f	14	SCLC	Chemotherapy	21	Alive
Nayman et al. [58]	60	f	0	NSCLC			
Jain et al. [59]	66	f	0	SCLC			
Kumar et al. [60]	57	m	0	NSCLC	Surgery		

f = female; m = male; mo; months; NSCLC = nonsmall cell lung carcinoma; SCLC = small cell lung carcinoma; y = years.

tor symptoms were the predominant initial presentations of ISCM. This is evident with the trend of discovering most of the cases through *postmortem* examination earlier and with imaging techniques later. However, some reported cases of primary lung cancer still present with ISCM as the initial finding [3–5].

Hematogenous spread, as stated above, is a proposed mechanism for metastasis, and the rich blood supply to the cervical spinal cord is expected to be responsible for increased incidence of regional involvement [6]. However, neither the cervical region nor the extent of multiregional metastasis appeared to affect survival in our review.

Many varied imaging techniques have been used to detect ISCM; however, magnetic resonance imaging proves to be an effective diagnostic strategy. Some reports have also found positron emission tomography–computed tomography to have a role in detecting ISCM [7,8].

Management of ISCM continues to be variable and experimental owing to the lack of experience and clinical study. Dam-Hieu et al. [9] proposed surgical intervention to significantly affect outcome; in our analysis, however, we did not observe whether surgery, radiation, or chemotherapy alone would change or improve survival. Using the multimodality approach with more than one intervention suggests improved median survival in this population. Although the multimodality treatment approach did significantly enhance the outcome, overall median survival continues to be grim at about 4 months. Hata et al. [10] showed an unexpected response to an oral tyrosine kinase inhibitor and radiation of more than 84 months.

Data collected in this review have significant limitations as they depend on retrospective collection performed by their respective authors and lack many details that would have affected the results of this analysis. ISCM has also been

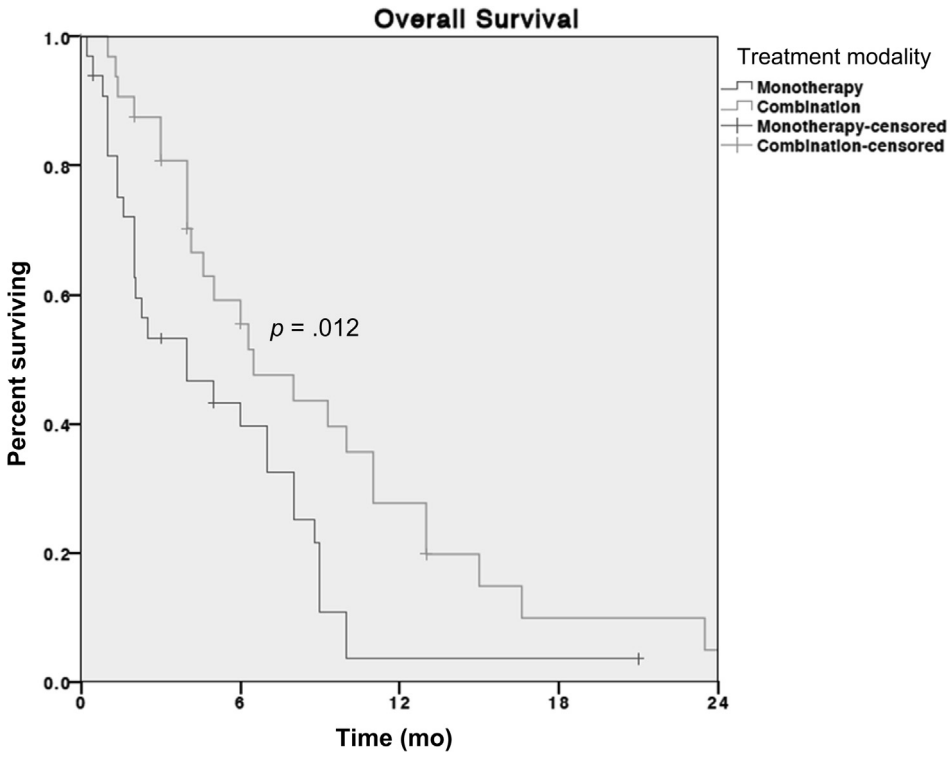

Fig. 1 Overall survival by treatment modality. mo = months.

an observed complication in other cancers such as breast cancer and our inclusion criteria of primary lung cancers, thus preventing a fully realized understanding of ISCM. A limited number of retrospective cases also prevent evidence-based practice and allows only observational recommendations. Despite these limitations, the review hopes to offer a comprehensive look at a poorly understood and rare metastatic process.

Conflict of interest

The authors have no conflicts of interests to report.

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