Skeletal Muscle Metastasis from Non-small Cell Lung Cancer

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Purpose

Skeletal muscle metastases (SMM) from non-small cell lung cancer (NSCLC) are rarely encountered in clinical practice. The prognosis and the adequate treatment are not known. The aim of the study was to report our experience and to make an extensive literature research concerning SMM.

Patients and Methods: In our unit, we identified 16 patients with SMM in a 10-year period. The source of our literature search (English and French language) was the international MEDLINE database, and it exhausted all cited publications.

Results: We found 114 cases in the international literature (follow-up period mentioned in 72 cases). Pain was the most frequent symptom (83%). A mass was palpable in 78% of cases. The diagnosis was obtained by either fine needle/surgical biopsy or wide ex-

eresis. The 5-year survival time was 11.5% with a median survival of 6 months. The 5-year survival rates: number of SMM - single versus multiple (13.6% [67 patients] versus 0% [21 patients]; p = 0.0022); disease-free interval (DFI) >6 months versus DFI :56 months (16.9% [18 patients] versus 9.1 % [70 patients]; p = 0.0458). We built three groups of prognostic significance: group I:

DFI >6 months and single metastasis; group II: DFI >6 months or single metastasis; and group III: DFI :56 months and multiple metastasis. The 5-year survival rates were: group I (14 patients): group II (57 patients):group III (17 patients) = 28%:6%:0% (p = 0.0000), and the median survival was 19:9:4 months.

Conclusion: The presence of SMM suggests an aggressive disease. Selection of patients for a local treatment is an important factor that determines survival. The ideal patient had a unique metachronous metastasic deposit that can be treated by surgery.

Key Words: Non-small cell lung cancer, Skeletal muscle metasta-sis, Surgery.

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ung cancer is the leading cause of cancer-related deaths. Non-small cell lung cancer (NSCLC) accounts for ap-

proximately 80% of all cases. Nearly 50% of cases will be metastatic at the time of diagnosis. The most common sites are the brain (10%), bones (7%), the liver (5%), and the adrenal gland (3%).1,2 When a metastasis is solitary in nature (regardless of the site), patients seem to have a better prognosis. Aggressive management has been asso-ciated with improved survival rates.3-6

Although the skeletal muscle accounts for nearly 50% of total body mass, metastatic disease is rarely encountered in clinical practice. Almost all publications in the international literature are case reports, and larger series of patients with lung cancer origin do not

exceed 10 cases,7-12

The purpose of this study is first to report our experi-ence and second to make an extensive review of all published cases in English and French literature concerning skeletal muscle metastasis (SMM) from NSCLC.

PATIENTS AND METHODS

Sixteen patients were discovered having SMM in our department more than a l0-year period (1998-2007). The diagnosis was obtained by fine needle biopsy or surgical specimen. For each patient, we collected: the demographic data and clinical symptoms, the muscle metastasis (site, number, size, and symptoms, disease-free interval (DFI), the histologic assessment of the tumors, the treatment applied for the lung cancer, and/or muscle metastasis. DFI was defined as follows: the interval between the primary NSCLC and the SMM; prevalent SMM was the situation when the muscular metastases were discovered before the primary NSCLC (these cases were included in the synchronous group of patients); synchronous = DFI ≤6 months; metachronous = DFI >6 months. Clinical staging of the disease was made according to the 1997 International Tumor, Node, Metastasis staging system,13

Literature Research

The source of our literature search was the international MEDLINE database, PubMed (a register of all publications in English and French) using the search items "SMM" or "muscle metastases" and "lung cancer" or "NSCLC." More-over, all the references listed from these articles were con-firmed (case reports, review articles, etc.). The research exhausted all cited publications.

Statistical Methods

We included all well-documented patients (in terms of follow-up) found in the international literature and in our practice. The

starting date for survival calculation was the diagnostic date of SMM. The probability of survival and different prognostic factors were calculated according to the Kaplan-Meier method for univariate analysis and the Cox proportional hazards model for multivariate analysis. A value of the $p < 0.05$ estimated by the log-rank test was regarded as significant. The statistical analysis was performed with SPSS software (SPSS Inc, Chicago, USA).

RESULTS

Our patients were 13 men and 3 women, averaging 60 years of age. Twenty-seven metastases were recorded: 7 in the muscles of the chest wall, 6 in the abdominal wall (Figure 1), 11 in the lower limb (Figures 2 and 3), and 3 in the upper limb. The patients' characteristics are listed in Table 1. The mean diameter (long axis) was 4 em. The primary lung tumor was treated anteriorly by surgery in two cases, chemotherapy in three cases, both surgery and chemotherapy in two cases and radio-chemotherapy in two cases. In all other cases, because of the short DFI (1 month) or prevalent muscle metastasis, chemotherapy was the chosen treatment. All patients died. The mean survival time was 5.6 months after the diagnosis of SMM and 8.7 months after the primary NSCLC.

Literature Search

According to the literature research, 114 cases of SMM have been described (period, 1946-2007). The patients' char-acteristics are detailed in Table 2. Most cases (97) were treated for a single muscle metastasis. Pain was the most frequent symptom (83%), and a mass was palpable in 78% of cases. The size varied largely between 1 and 20 em, median of 6 em. Local treatments were done in 80 cases.

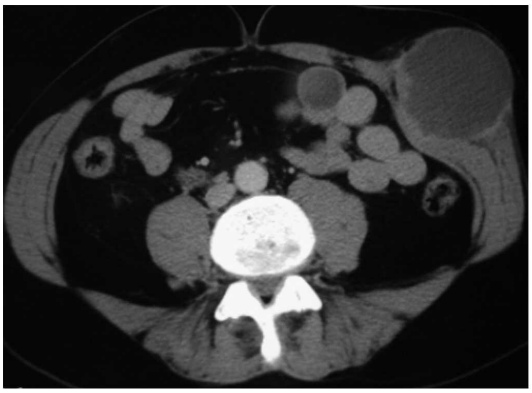

FIGURE 1. Computed tomography (CT) scan of a muscle metastasis in the abdominal wall (patient 5).

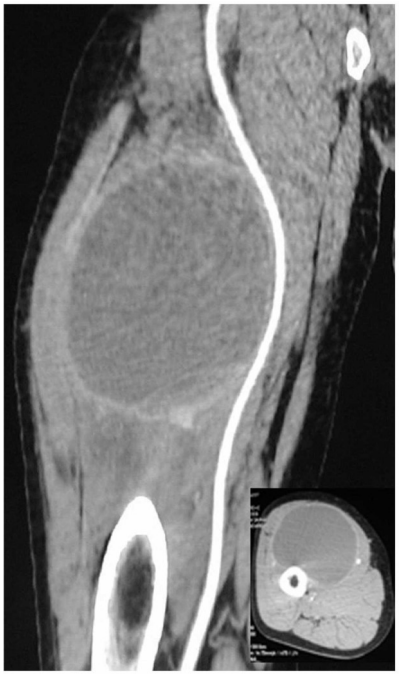

FIGURE 2. Computed tomography (CT) scan of a muscle metastasis in the lower limb (patient 6).

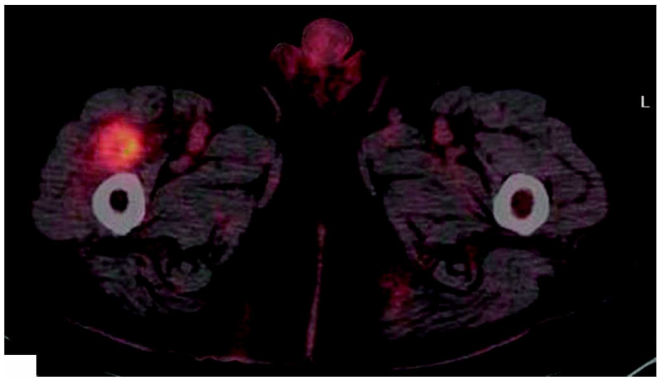

FIGURE 3.18 fluoro-deoxi-glucosis positron emission tomoscintigraphy-scan of a muscle metastasis in the lower limb (patient 11).

TABLE 1. Patient's Characteristics

No./Gender/Age	Symptoms	Size (cm)	DFI (mo)	TN	Histology	Treatment		Survival (mo)
						Local	General	
1/M/67	P + M	5	7	T4N2	SqCC	—	CTh	7
2/M/69	P + M	9	4	T2N3	ADC	S + RTh	CTh	5
3/F/66	P	3	10	T3N1	SqCC	RTh	CTh	17
4/F/45	P	7	2	T3N2	SqCC	—	—	1
5/M/51	P + M	4	2	T2N1	SC	S	CTh	13
6/M/46	P + M	6; 5	1	T2N2	SC	S	CTh	3
7/M/66	P + M	5	pMM	T2Nx	ADC	—	—	1
8/M/52	M	12	pMM	T4Nx	SqCC	S + RTh	CTh	3
9/M/71	M	5	3	T1Nx	SC	S	CTh	3
10/M/75	M	5;3	3	T2N2	LCC	—	CTh	2
11/M/65	P + M	2;2	pMM	FNB	Undif	—	CTh	3
12/M/54	M	5; 2; 2; 1; 1	1	T2N3	ADC	—	CTh	3
13/M/60	—	3	8	T2N0	ADC	—	CTh	8
14/F/50	—	3;2;2	8	T2N2	ADC	—	CTh	9
15/M/46	P + M	3;2;2	pMM	T3N1	ADC	RTh	CTh	7
16/M/84	P + M	4	pMM	T2Nx	ADC	S + RTh	CTh	6

P, pain; M, mass; DFI, disease free interval; pMM, prevalent muscle metastasis; TN, TN staging; S, surgery; CTh, chemotherapy; RTh, radiation therapy; SqCC, squamous cell carcinoma; ADC, adenocarcinoma; SC, sarcomatoïd carcinoma; LCC, large cell carcinoma; Undif, undifferentiated non-small cell lung cancer.

Statistical Analysis

The follow-up period was recorded for only 72 cases in the international literature. Including ours, it made an 88-patient statistical database. The I-year and 5-year survival rates were 32.6% and 11.5%, respectively, with a median survival of 6 months (Figure 4). The following parameters did not significantly influence the sur-

vival of patients: age, sex, presence of symptoms, site and size of metastasis, histology, and TN staging of the NSCLC. The survival rate was influenced by the number of SMM: single versus multi-ple (13.6% [67 patients] versus 0% [21 patients] at 5 years; $p = 0.0022$) (Figure 5) and DFI >6 months versus DFI ::;6 months (16.9% [18 patients] versus 9.1% [70 patients] at 5 years;p = 0.0458) (Figure 6). In the multivariate analysis, the single metastasis ($p = 0.0016$; 95% confidence interval: 1.43-4.73) and a DFI >6 months ($p = 0.0339$; 95% confidence interval: 0.26-0.94) maintained the statistical significance. Us-ing these two independent factors of prognostic significance, we built three groups: group I: no risk factors (DFI >6 months and single metastasis), 14 patients; group II: one risk factor (DFI >6 months or single metastasis), 57 patients; and group III: two risk factors (DFI ::;6 months and multiple metasta-sis), 17 patients. The 5-year survival rates were group I:group II:group III = 28%:6%:0% ($p = 0.0000$) (Figure 7) and the median survival, 19:9:4 months.

We evaluated the prognostic significance of the treat-ments applied. When local treatment was applied (with or without chemotherapy), the 5-year survival was 14.4% (68 patients); when only chemotherapy or supportive care was done, the 5-year survival rate was 0% (20 patients) ($p = 0.0000$). Comparing the local treatments, we had the follow-ing survival rates at 5 years: surgery (17 patients) versus radiotherapy (40 patients) versus combination (surgery + radiotherapy) (11 patients) = 28% versus 14.5% versus 0% ($p = 0.5156$).

DISCUSSION

According to Prior,14 the first description of muscle metastasis was reported by Wittich in 1854, and Willis was the first to report a muscle metastasis of lung origin. Despite being highly vascular, the exact incidence is barely known. In 1950, Abrams et a1.l[5] failed to mention this tissue as a site of metastasis in his thorough study of 1000 consecutive autop-sied cases. Willis[l6] observed only four instances in 500 cases of carcinoma. Subclinical metastasis may indeed be more com-mon than generally thought. One large autopsy study of 5298 people found that 6% involved SMM of the chest or abdominal wallP Acinas-Garcia et a1.l[8] reported an incidence of 17.5%. Pearson[l9] systematically studied several muscles, arbitrarily chosen, and he found a 16% incidence of SMM.

Nowadays autopsy on all cancer-related deaths is not performed routinely. An important help is the 18 fluoro-deoxi-glucosis positron emission tomoscintigraphy-scan mostly for detecting subclinical metastasis.[2o],21 Since 2004 when this imaging procedure was introduced into our practice, single SMM has been rarely seen. Certainly, there are several limitations concerning muscle enhancement in PET scan, so we included in our study only the patients with computed tomography (CT)-scan confirmation and a histologic sample of one metastatic deposit.

There are several theories explaining muscle resistance of metastatic disease. The most important hypotheses are mechanical (muscle contraction, high tissue pressure, II and extremely variable blood flow22), metabolic (pH, lactic acid production,23 and toxic-free radical oxygenll) or immuno-logic (cellular and humoral immunity and hypersensitivity

TABLE 2. Literature Search and Patient's Characteristics

Characteristics	Value	No. cases
Age	Median	58
	Range	31–81
Sex	Male	89
	Female	17
		8 NR
Number	Single	97
	2/3/4	8/5/2
	Multiple	2
Site	Abdominal wall	22
	Chest wall	20
	Upper limb	33
	Lower limb	55
		9 NR
Symptoms	Mass	78
	Pain	83
		14 NR
DFI	Prevalent	53
	Synchronous ≤6 mo	19
	Metachronous >6 mo	20
		22 NR
Diagnosis	Fine needle biopsy	53
	Surgical biopsy	23
	Wide exerexis	22
		16 NR
Histology	SqCC	43
	ADC	48
	SC	3
	LCC	4
	NSCLC	10
		6 NR
Treatment	Surgery	24
	Radiation therapy	46
	Combination	9

NR, Not recorded; DFI, disease free interval; SqCC, squamous cell carcinoma; ADC, adenocarcinoma; SC, sarcomatoid carcinoma; LCC, large cell carcinoma; NSCLC, non-small cell lung cancer.

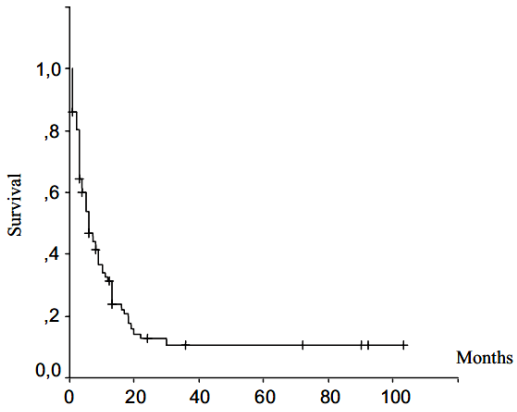

FIGURE 4. Overall survival rate.

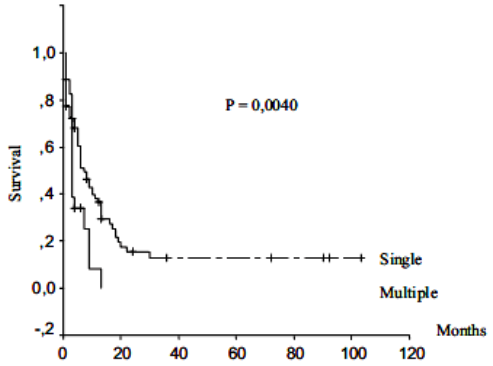

FIGURE 5. Overall survival rates according to the number of muscle metastasis.

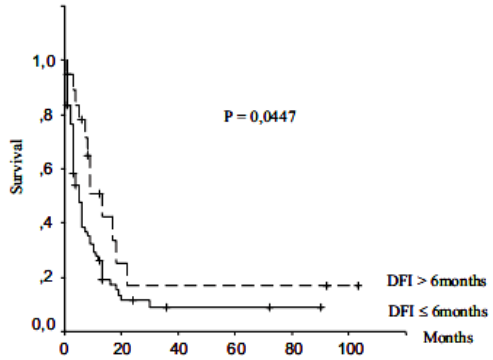

FIGURE 6. Overall survival rates according to the disease-free interval (DFI).

reaction[24]). None of them can explain the full mechanism but perhaps a combination of them.

The aim of this extensive review is to define the clinical course and prognosis of SMM and what treatment should be use. Almost 1/3 of metastases, in our experience, were discovered before the lung cancer. In the international literature V2 of metastasis are prevalent, 1/4 synchronous, and only V4 were discovered more than 6 months after the treatment of the primary NSCLC. These findings

can be an argument for particularly aggressive cancers. Most SMMs are clinically palpable and painful. Histologic samples are easily obtained under local anesthesia.

The most common appearance (83%) of the lesions on contrast-enhanced helical CT is that of a rim-enhancing mass with central hypoattenuation.[25],26 Intramuscular abscesses can have similar appearance, but the presence of acute focal clinical findings, bacteremia and sepsis, clinical history of intravenous drug abuse, and abscess is the likely diagnosis. In the absence of clinical findings, CT detection of these lesions may guide needle biopsy.

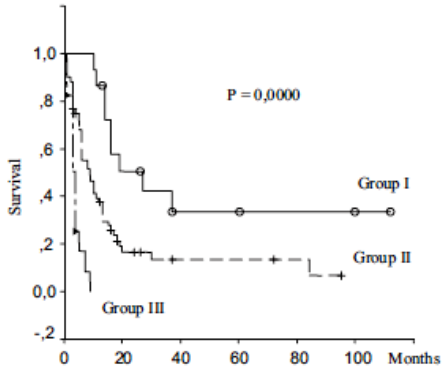

FIGURE 7. Overall survival rates according to prognostic factors.

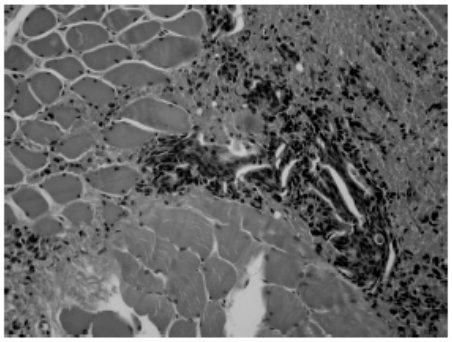

FIGURE 8. Muscle metastasis of lung adenocarcinoma.

Magnetic resonance imaging is the technique of choice to characterize soft tissue lesion, but the metastatic lesions show nonspecific characteristics: increased signal intensity relative to skeletal muscle on T2-weighted images, decreased signal intensity on Tl-weighted images, and heterogenous enhancement after gadolinium administra-tion.27-3o The same characteristics apply to soft tissue sar-coma. Although solitary muscle metastasis are rare, the combination of a muscle mass with a solitary lung mass with or without adenopathy is more likely to represent a lung cancer metastasizing to the muscle. When patients with sarcoma have shown lung metastasis, there has been usually more than one lesion.

Almost all type of NSCLC can metastasize in the muscle with no particular preferences (Figure 8). The prog-nosis is obscure, most of the patients died with a median

survival of only 6 months. The role of local treatment in the global survival is difficult to define. Surgery and/or radiother-apy were applied because of the absence of other metastatic deposits (the primary tumor being controlled). Otherwise, for extensive disease, the patients benefited only chemotherapy or supportive care. Our results showed that a particular set of patients could benefit from local treatment if they had no risk factors (single metastasis, DFI >6 months), with a median of survival of 19 months. We found a slight difference (not of statistical significance) of survival in the advantage of surgery.

There are several bias in our results because: most of the reports are case reports, sometime with incomplete data, rare pathology, and only 114 published cases in a 60-year period (so difficulty to conduct a prospective study). Despite that the present analysis gives some information of the clinical and prognostic behavior of the SMM from NSCLC. Half of them are prevalent painful masses. The presence of SMM suggests an aggressive disease.

Selection of patients for a local treatment is an important factor that determines survival. Unfortunately, the tumor and host factors that allow local treatment to control a systemic disease are unknown. Despite the limitations of a small study group, the ideal patient had a unique metachronous metastasic deposit that can be treated by surgery; in that case 1/4 of patients are still alive after 5 years.

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