

Soft tissue metastases in lung cancer: a review of the literature

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Abstract. – BACKGROUND: In lung cancer patients, metastases to soft tissues (STs), including skeletal muscle, subcutaneous tissue and skin, are rarely reported. Besides, lung cancer, primary carcinomas of the kidney and colon are the most commonly associated with ST metastases.

AIM: To determine the prevalence, clinical-pathological features and treatment options of ST metastases originating from lung carcinoma.

MATERIALS AND METHODS: A literature search was performed using the following terms: lung cancer, ST metastasis, skeletal muscle metastasis, cutaneous metastasis, subcutaneous metastasis.

RESULTS: Autopsy series have detected STs metastases in 0.75-9% of patients who died from metastatic lung carcinoma. Pain and the presence of a palpable mass are the most frequent clinical features. The biopsy is recommended after MRI for diagnosis. Due to the rarity of ST metastases, the differential diagnosis must be posed especially with primary ST sarcomas. The type of treatment depends on the patient's clinical status and prognosis, and includes observation, radiotherapy, chemotherapy and surgery.

CONCLUSIONS: In lung cancer patients, ST metastases are rare, but not exceptional. Their presence should be suspected in the presence of a palpable mass either painful or asymptomatic. Radiological and histological examinations are required for the definite diagnosis. The choice of treatment should be based on considerations related to the stage of the primary tumor and the patient's global health status.

Key Words:

Bronchogenic carcinoma, Soft tissue, Metastasis, Skeletal muscle.

to lung cancer¹. Approximately 50% of cases are metastatic at the time of diagnosis, and 60% of patients have microscopic or clinically evident metastasis at the time of primary tumor treatment^{1,2}. Lung cancer can metastasize to any organ; *post-mortem* studies have reported a prevalence of metastatic localizations in up to 93% of lung cancer patients with end-stage disease³⁻⁵. Major sites of metastases include liver (33-40%), adrenal glands (18-38%), brain (15-43%), bone (19-33%), kidney (16-23%), and abdominal lymph nodes (29%)⁶⁻⁸. Metastases to soft tissues (STs), including skeletal muscle, subcutaneous tissue and skin, are rarely reported in the literature, although the skeletal muscle accounts for nearly 50% of total body mass^{9,10}.

Epidemiology

The first description of a muscle metastasis was provided by Wittich in 1854, and Willis was the first to report a muscle metastasis of lung origin¹¹. There are several case reports on the subject, but only few large case series. Therefore, no definite guidelines on the management of patients with ST metastases of lung origin are currently available¹⁰⁻¹⁴. Autopsy series reported ST metastases in 0.75-9% of patients who died from metastatic carcinomas¹⁵⁻¹⁷. The prevalence of skeletal muscle metastasis (SMM) in autopsy series of patients with any cancer ranges from 0.8% to 17.5%¹⁸⁻²¹, whereas skin metastasis are reported in 0.75-9% of cases¹⁵. Studies in lung cancer patients have revealed a lower prevalence of cutaneous (1.3-4%)^{5,6} and muscular metastases (0-0.8%)^{11,13,14,21,22}. However, subclinical metastases may be more frequent than commonly believed¹¹.

The lung is the most common primary carcinoma leading to clinically recognized ST metastases, followed by kidney and colon cancers^{10,23}. Nguyen et al⁹ indicated that the prevalence of ST

Introduction

Lung cancer is the leading cause of cancer-related deaths¹. Over 157,000 new cases and 142,000 deaths per year in the U.S. are attributed

metastasis originating from lung carcinoma (2.3%) was much lower compared with that of melanoma (9.8%). Mignani et al²⁴ suggested that the primary tumor most frequently metastasizing to the skeletal muscle is renal cell carcinoma, followed by gastrointestinal tract cancers and bronchogenic carcinomas. Noteworthy, cancers commonly metastasizing to the bone such as prostate, breast and thyroid cancers, only exceptionally disseminate to STs¹⁰.

Pathogenesis

Several theories have been proposed to explain the “resistance” of skeletal muscle to metastatic diseases²⁵⁻²⁹. The mechanical hypothesis postulates that muscle contractions may act protectively by inducing a high tissue pressure²⁵ and variable local blood flow³⁰. In a mouse study, Weiss³¹ found that the survival of tumor cells injected into the muscle was shorter in electrically stimulated muscles relative to denervated or non-contraction control tissues. This finding suggests that muscle contractions could prevent metastatic cell survival within the tissue. Although limb skeletal muscle accounts for approximately 40% of the weight of an average adult³² and is perfused by a rich capillary system, blood flow is highly variable in the contractile state and is under the extrinsic influence of β -adrenergic receptors³³. In contrast, sites of frequent metastases, such as the liver and bones, are characterized by high perfusion and constant blood flow³⁴. During physical exercise, muscle capillaries dilate and the amount of blood delivered increases up to 800 folds relative to the resting state³³. Moreover, mesenchymal tissues, including the skeletal muscle, possess diffusible proteases and other enzyme inhibitors that can block enzyme-dependent processes of invasion or tumor development²⁵. Finally, blood flow turbulences may destroy circulating tumor cells³⁴.

The metabolic hypothesis highlights the role of local pH, lactic acid production²⁹, and reactive oxygen species (ROS) generation²⁵. Researchers have also proposed that tumor cells may actively “select” growth environments rather than being passively lodged in metastatic tissues by chance of embolization²⁵. Characteristics intrinsic to skeletal muscle, such as elevated lactate production, pH instability and variable oxygen tensions, may create a milieu unfavorable to the development of macroscopic tumor foci, thus making them clinically undetectable^{20,29}. Of interest, factors such as traumata can alter these microenvi-

ronments by the release of growth-promoting factors or fibrin clots that may act as trapping sites for circulating tumor cells^{35,36}.

Finally, the immunologic hypothesis points on the cellular and humoral immunity and hypersensitivity reactions³⁷. According to this hypothesis, lymphocytes and natural killer cells residing within the skeletal muscle would play a major role in the inhibition of metastatic cancer cell growth^{25,34}.

Routes of Dissemination

Several pathophysiological mechanisms of intramuscular metastatic spread have been proposed. The hematogenous route is considered to be the most important pathway. The detection of arterial emboli consisting of tumor cells confirms this hypothesis¹⁵. Malignant tumors can also metastasize into the musculature via venous vessels, especially through the paravertebral venous plexus³⁸. Some Authors have proposed that muscle metastases can originate in intramuscular aberrant lymph nodes^{37,39}. In particular, metastasis in the psoas muscle might arise in the psoas lymph nodes located between the musculature and the spine^{24,37}. Furthermore, SMMs can result from perineural spread. Interestingly, metastases to muscles can occur after muscle traumata⁴⁰. Magee and Rosenthal⁴¹ suggested that skeletal muscle injuries may alter the local physiology, resulting in increased susceptibility to developing metastatic diseases.

Clinical Presentation

Pain is the most frequent symptom (83%), and a mass is palpable in 78% of cases of ST metastases³⁰. Others modes of presentation include a painless soft tissue lump in patients with occult primary tumors¹⁰, asymptomatic masses, accidental diagnosis after a trauma involving the affected area, weight loss or a single metastasis in a patient with unknown tumor. It should be noted that non-small-cell lung carcinoma, when arising peripherally, most commonly presents without pulmonary symptoms²³. The clinical features of a metastatic carcinoma to STs can mimic a sarcoma. However, a painful mass is more commonly observed in patients with ST metastasis than in primary sarcomas¹⁴. The size of the lesion usually ranges between 1 and 20 cm (median of 6 cm)³⁰. The most frequently reported locations of ST metastases include the back, chest wall, abdomen, thigh muscles, ileopsoas muscle and paraspinous muscles (Figure 1; Table I)^{13,14,16,23,30,42,43}.

Damron and Heiner²³ showed that ST metastases can occur in many muscular and subcutaneous districts across the body with a ratio higher than 1.5:1. Others reported a ratio of 1.2:1, suggesting that subcutaneous ST metastases may have been under-reported in the literature⁹. One explanation for this discrepancy could be that subcutaneous lesions tend to be smaller than muscular localizations. Another potential reason is that 5/19 (26%) of subcutaneous lesions were 1 cm or less in size which may represent a limitation for diagnostic computed tomography (CT) and magnetic resonance imaging (MRI) scans⁹ or because they are less symptomatic than bone metastases²³.

Diagnosis

Due to the rarity of ST metastases, the differential diagnosis must be posed with primary ST sarcomas¹⁰ and primary muscle lymphomas²¹ as well as with several benign diseases, such as muscle haemangiomas, intramuscular ganglia and myxomas^{27,44}. In addition, ischiogluteal bursitis can mimic muscle metastases both clinically

and radiologically²⁸. Notably, ischiogluteal bursitis occurs frequently in cancer patients²⁹.

Surov et al²¹ showed that 32.5% of identified SMMs appeared as abscess-like intramuscular lesions. Furthermore, secondary muscle abscesses can occur within metastases, while 3.7% of muscle metastases present with multiple intramuscular calcifications that can mimic benign muscle calcifications, such as those occurring in myositis ossificans, calcific tendinitis, angiomas, systemic sclerosis, and calcific myonecrosis.

Although magnetic resonance imaging (MRI) is not specific for ST metastasis, it has been advocated as an indispensable tool for the diagnosis and treatment planning in patients with ST malignancies⁴⁵. MRI has become the preferred technique for distinguishing ST metastases from sarcomas and other ST lesions³⁹. In ST metastases, MRI scans typically show lesions with poorly defined margins, low signal intensity on T1-weighted sequences, high signal intensity on T2-weighted sequences, and enhancement with gadolinium^{20,24}. Surrounding edema is common. Erosion of the adjacent bone is rarely evident in

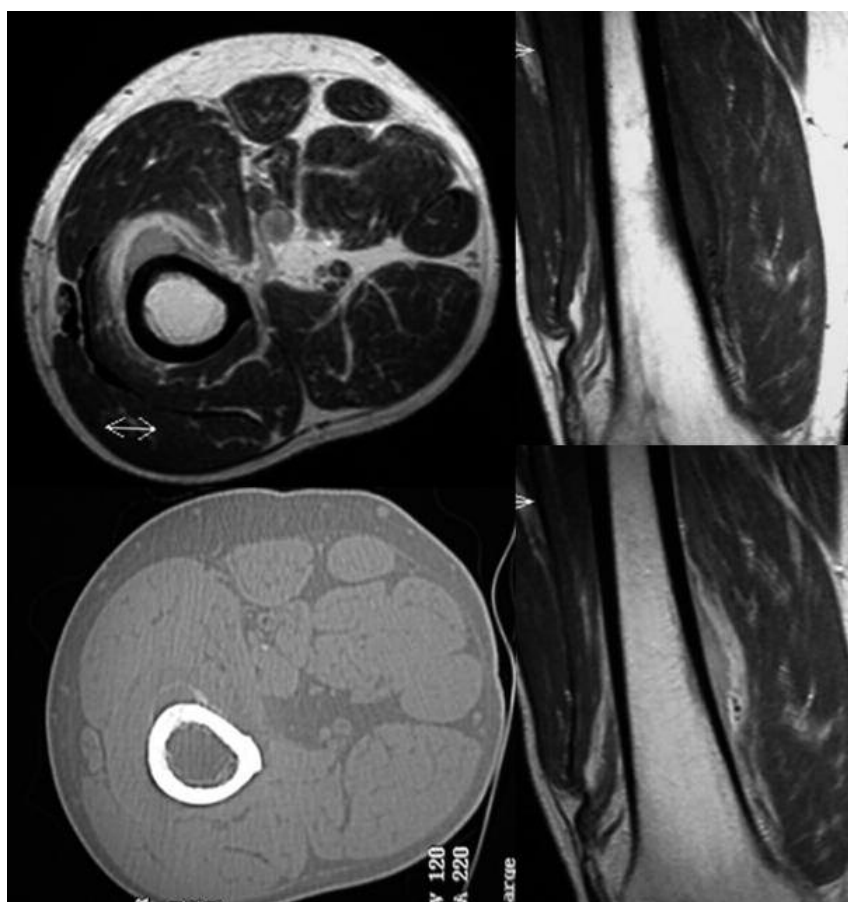


Figure 1. Soft tissue metastasis located close to the femur in a lung cancer patient. The CT scan shows the presence of perilesional calcification, with sparing of the bone cortex. The MRI scan shows the lesion and perilesional edema.

Table I. Sites of localization of soft tissues metastasis in patients affected by lung carcinoma.

	Back		Chest				Abdominal wall		Upper limb					Lower limb			
	Paraspinal cervical muscles	Paraspinal lumbar muscles	Chest wall	Pectoral muscle	Inguen				Scapula	Shoulder	Biceps, triceps muscle	Brachialis muscle	Finger	Thigh	Quad	Buttock	Calf
Damron et al (12 cases)	1	1	1	1	1	/	/	/	/	/	2	1	1	1	1	1	/
Pop et al (16 cases)	/	/	7	/	/	6			3					11			
Plaza et al (14 cases)	5		2	/	/	/	/	/	2	1	1	/	/	2	/	1	/
Tuoheti et al (4 cases)	/		/	/	/	/	/	/	/	/	/			2	/	/	2

MRI scans²⁴. Wide peritumoral enhancement with central necrosis is one of the main feature of SMMs, and is detectable in 92% of cases¹⁴. Technetium-99m-labeled nuclear scan can show increased uptake within the ST mass¹⁴. Surov et al²¹ have described five different types of SMMs based on computed tomography (CT) findings: focal intramuscular masses with homogeneous contrast enhancement (type I); abscess-like intramuscular lesions (type II); diffuse metastatic muscle infiltration (type III); multifocal intramuscular calcification (type IV); and intramuscular bleeding (type V). The largest proportion of SMMs presents as intramuscular masses (type I, 52.5%). Of these, 60% of lesions presents as a single mass and 40% as multiple localizations²¹. In ST sarcomas, MRI with gadolinium provides information about shape, size and vascularity of the lesions and its relationship with nerves and/or blood vessels. Most importantly, this technique allows to define the nature of the mass and to plan its resection. Most of connective tissue sarcomas display low signal intensity on T1-weighted sequences and high signal intensity on T2-weighted sequences. The increased vascularity and the presence of fat within sarcomas can render these tumors hypointense in both T1- and T2-weighted sequences. In contrast, dense lesions, such as desmoid cysts or fibrosarcomas, may appear hyperintense in both sequences⁴⁶.

A recent study showed that fluorine-18 fluorodeoxyglucose positron emission tomography/CT (F-18 FDG PET/CT) had higher sensitivity than MRI in detecting skin and ST metastases⁴⁵. This is supportive of the increasing role of F-18 FDG PET/CT in cancer patient management⁴⁰ and of the ability of this technique to detect subclinical metastases^{33,46}. Nevertheless, false positives are possible, as observed in two cases (actinic keratosis, skin folding) reported by Nguyen et al⁹.

PET/CT is also highly sensitive for the detection of ST sarcomas. In such cases, PET/CT is especially useful in seeking metastases, additional lesions or lymph node localizations⁴⁶.

Because of the variety of clinical and radiological manifestations, misdiagnosis of SMMs is not infrequent. Hence, although it is important to be aware of the various imaging patterns of SMMs, only the histologic examination allows the definite diagnosis. The biopsy is therefore essential to gather key diagnostic information to guide subsequent treatment and should be performed after MRI^{14,23,33}.

Treatment

The treatment of ST metastases depends on their localization and clinical presentation as well as on the prognosis related to the primary tumor. Therapeutic options include observation, radiotherapy, chemotherapy, and surgery. For painful masses in the context of a widespread metastatic disease, radiotherapy or chemotherapy or both may be indicated based on the primary tumor, the organ involved, the extent of involvement, symptoms attributable to the various sites, the patient's age, health status and goals²³. Radiotherapy is efficacious in controlling pain and size of the lesion, but can cause relevant complications such as burns and muscle contractures¹⁴, and it is usually indicated in upper limb ST metastases not involving the neurovascular bundle (Figure 2).

Surgical excision may be indicated for isolated lesions after a long disease-free interval, in tumors with good prognosis or after an appropriate treatment of the primary tumor²³. Surgery can be associated with radiotherapy performed before or as an adjunct to surgical treatment²³. In selected cases, the excision not only reduces pain but can also improve prognosis¹⁴. For non-solitary metastases, palliative treatment with surgical debulking is indicated if pain and neurovascular damage are becoming clinically significant¹². In our experience, lower limb localizations more frequently constitute indications to surgery relative to upper limb lesions.

Prognosis

The presence of ST metastases influences the treatment of the primary tumor. In fact, in the case of metastatic lung cancer, surgical excision of the primary lesion is not indicated, and the patient is usually treated with chemotherapy only^{9,47}. Studies have reported that the survival of patients with ST metastases ranges from less than 9 months to not more than 3 years after the diagnosis of the mass, although in some cases survival up to 5 years has been reported²³. A solitary metastasis in the interosseous membrane of the lower limb was associated with 2 years survival following surgical treatment (Figure 3 A-H)⁴⁸. The presence of a skin metastasis in a lung cancer patient indicates a poor prognosis, with a median survival of 2-4 months^{16,42,43}.

Conclusions

In patients with lung cancer, metastatic dissemination to STs is infrequent, but not exceptional. The presence of ST metastases should be suspected in lung cancer patients presenting with painful or asymptomatic palpable masses. The identification of ST metastases has a relevant impact on the management and prognosis of lung cancer patients. The diagnosis is based on imaging techniques, especially MRI, CT and F-18 FDG PET/CT. However, the confirmation of diagnosis is based on the histological examination

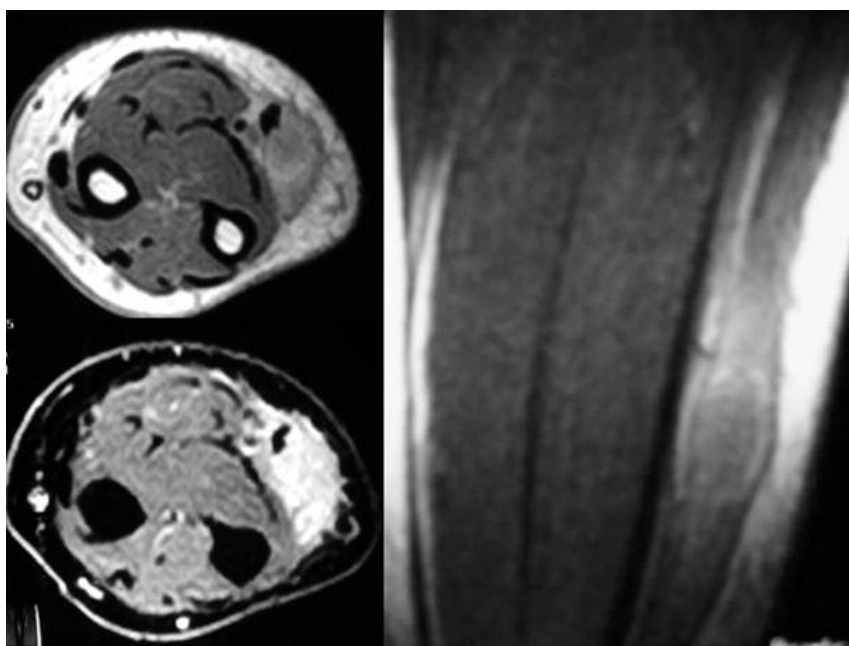


Figure 2. Soft tissue metastasis located into the ulnar carpal flexor muscle in a lung cancer patient.



Figure 3. Localization of metastatic lung carcinoma in the interosseous membrane. **A-B**, X-ray showing periosteal reaction in the distal third of the fibula. **C-F**, T1- and T2-weighted MRI scans showing that the lesion is strictly close to the fibula. The coronal plane MRI scan shows that the distal margin of the lesion is located more than 2 cm above the articular surface. **G-H**, Postoperative X-ray showing the tibiofibular reconstruction after type 2 resection according to Capanna.

of bioptic or excisional specimens. Treatment options for ST metastases include radiotherapy, chemotherapy, surgical removal as well as combined approaches. Treatment should be tailored to the nature and extent of the primary tumor, the presence of metastases involving other organs/tissues, the patient's age, the global health status and therapeutic goals.

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