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CLINICAL & BASIC RESEARCH

Skeletal Muscle Metastasis from Renal Cell Carcinoma

21 cases and review of the literature

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نقيلة العضلة الهيكلية من سرطان الخلايا الكلوية

21 حالة ومراجعة الدراسات المنشورة

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ABSTRACT: ***Objectives:*** This study aimed to raise radiologists' awareness of skeletal muscle metastases (SMM) in renal cell carcinoma (RCC) cases and to clarify their imaging appearance. ***Methods:*** A retrospective analysis was undertaken of 21 patients between 44–75 years old with 72 SMM treated from January 1990 to May 2009 at the MD Anderson Cancer Center in Houston, Texas, USA. Additionally, 37 patients with 44 SMM from a literature review were analysed. ***Results:*** Among the 21 patients, the majority of SMM were asymptomatic and detected via computed tomography (CT). Mean metastasis size was 18.3 mm and the most common site was the trunk muscles (83.3%). The interval between discovery of the primary tumour and metastasis detection ranged up to 234 months. Peripheral enhancement (47.1%) was the most common post-contrast CT pattern and non-contrasted CT lesions were often isodense. Magnetic resonance imaging (MRI) characteristics were varied. Five lesions with available T1-weighted pre-contrast images were hyperintense to the surrounding muscle. Other organ metastases were present in 20 patients. Of the 44 SMM reported in the literature, the majority were symptomatic. Average metastasis size was 53.4 mm and only 20.5% of SMM were in trunk muscles. The average interval between tumour discovery and metastasis detection was 101 months. Other organ metastases were recorded in 17 out of 29 patients. ***Conclusion:*** SMM should always be considered in patients with RCC, even well after primary treatment. SMM from RCC may be invisible on CT without intravenous contrast; contrast-enhanced studies are therefore recommended. SMM are often hyperintense to the surrounding muscle on T1-weighted MRI scans.

Keywords: Renal Cell Carcinoma; Skeletal Muscle; Metastasis; United States.

الملخص: الهدف: تهدف هذه الدراسة إلى زيادة وعي أخصائي الأشعة عن نقيلة العضلة الهيكلية في حالات سرطان الخلايا الكلوية وتوضيح مظاهر صورها الأشعاعية. **الطريقة:** تم إجراء تحليل إستعادي على 21 مريضا أعمارهم بين 75–44 سنة لديهم 72 حالة معالجة لنقيلة العضلة الهيكلية من يناير 1990 إلى مايو 2009 في مركز أندرسون للسرطان في هيوستن، تكساس، الولايات المتحدة الأمريكية. بالاضافة إلى ذلك، تم تحليل 37 مريضا لديهم 44 حالة نقيلة العضلة الهيكلية من الدراسات المنشورة. **النتائج:** من بين 21 مريضا، كان معظم سرطان الخلايا الكلوية عديم الأعراض وتم كشفه عن طريق الأشعة المقطعية. متوسط مقاس النقيلة كان 18.3 ملم وكان أكثر موقع شيوعا هو العضلات الجذعية (83.3%). الفترة بين اكتشاف المرض الأولي وكشف النقيلة امتدت إلى 234 شهرا. استعزاز الحافة (40%) كان أكثر الأنماط شيوعا في الأشعة المقطعية المتباينة، وكانت الآفات عادة بذات الكثافة في الأشعة المقطعية المتباينة. خصائص التصوير بالرنين المغناطيسي كانت متعددة. خمسة آفات كانت مفرطة الكثافة مقارنة بالعضلات المحيطة في الصور الموزونة T1 قبل التباين. نقيلة الأعضاء الأخرى كانت موجودة في 20 مريضا. من بين 44 حالة نقيلة العضلة الهيكلية المنشورة في الأدبيات، كان معظمها عرضية. متوسط مقاس النقيلة كان 53.4 ملم و 20.5% من النقيلة كانت في العضلات. الجذعية متوسط الفترة بين أكتشاف الورم وكشف النقيلة كانت 101 شهرا. نقيلة الأعضاء الأخرى كانت مسجلة في 17 من أصل 29 مريضا. **الخلاصة:** نقيلة العضلات الهيكلية يجب أن تؤخذ في الاعتبار في مرضى سرطان الخلايا الكلوية، حتى بعد مرحلة العلاج الأولي. نقيلة العضلة الهيكلية من سرطان الخلايا الكلوية ربما تكون غير مرئية في الأشعة المقطعية بدون التباين الوريدي، لذا يوصى بدراسات استعزاز التباين. نقيلة العضلة الهيكلية عادة مفرطة الكثافة مقارنة بالعضلة المحيطة في تصوير الرنين المغناطيسي الموزونة T1.

مفتاح الكلمات: سرطان الخلايا الكلوية؛ العضلة الهيكلية؛ نقيلة؛ الولايات المتحدة الأمريكية.

Advances in Knowledge

- *The findings of this study suggest that relatively small and asymptomatic skeletal muscle metastases of the trunk in patients with renal cell carcinoma (RCC) are usually detected by re-staging computed tomography (CT).*
- *Furthermore, skeletal muscle metastases among the studied RCC patients were often hyperintense to the muscle on pre-contrast T1-weighted magnetic resonance images and invisible or barely visible on CT images without contrast.*
- *A marked male predominance was observed among the studied RCC patients with skeletal muscle metastases.*

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Application to Patient Care

- *As indicated by the results of this study, radiologists interpreting re-staging CT scans of patients with RCC should be alert for signs of possible muscle metastases.*

Renal cell carcinoma (RCC) comprises nearly 90% of all malignant renal neoplasms and the metastatic potential of this cancer is widespread and unpredictable.[1] While metastasis to the skeletal muscles is considered unusual, RCC is among the more common primary tumours to metastasise to this type of muscle tissue.[2–5] In a review of over 2,000 patients with metastatic solid tumours, Surov *et al*. found that 2.3% of those with RCC had skeletal muscle metastases.[6] The location of skeletal muscle metastases can vary widely. Furthermore, they may be painless and can sometimes occur long after the primary surgical treatment; therefore, discovering these metastases can be challenging. In order to reduce the chance of overlooking muscle metastases, the possibility of their presence should be considered in patients with a history of RCC, even long after the primary tumour has been resected.[7]

Methods

A retrospective analysis was undertaken of 21 patients between 44–75 years old with 72 skeletal muscle metastases treated from January 1990 to May 2009 at the MD Anderson Cancer Center in Houston, Texas, USA. Demographic, diagnostic, clinical and radiological data and patient outcome information were collected from teaching files and retrospectively reviewed and analysed. Cases were reviewed with regard to age; gender; presenting symptoms; time of diagnosis; histopathological subtype of the primary tumour; time of initial discovery of the skeletal muscle metastases; first time the muscle metastases were visible on retrospective review; evidence of skeletal muscle and other metastases; and patient outcome. Skeletal muscle tumours seemingly caused by the direct extension into the skeletal muscles of the cancer from the kidneys or from other metastases were not included. Only metastases presumed to have spread haematogeneously were included in the analysis. Diagnoses were made from clinical, pathological and radiological data.

Images from computed tomography (CT) and magnetic resonance imaging (MRI) from the time the skeletal muscle metastases were first reported were examined by two radiologists to evaluate the site, size, shape, CT density and MRI characteristics (including MRI signal intensity, pattern of enhancement and any other special features) of the metastases. In some cases, individual skeletal muscle metastases were never mentioned in the radiological reports. In these cases, the radiologists determined the earliest imaging study on which the metastases were visible. When additional skeletal muscle metastases appeared after the initial discovery, up to eight lesions per patient were also included in the analysis. When more than eight muscle metastases were present, the largest eight lesions were evaluated. MRI signal intensity and CT density were compared with those of the adjacent muscles. Imaging characteristics were determined by consensus between the two radiologists.

Additionally, a literature review was also conducted to include 37 patients with 44 skeletal muscle metastases in the analysis. Journal articles for the literature review were identified by searching the MEDLINE®/PubMed database for articles containing the words "metastasis" and "muscle" in the title. Other relevant articles cited in the bibliographies of these articles were also included. The literature review was limited to articles published in English, French or German. The cut-off point for the review was March 2013.

This study was performed in accordance with institutional policies and approved by the Institutional Review Board of The University of Texas, MD Anderson Cancer Center.

Results

The demographic characteristics and CT imaging characteristics of the muscle metastases for the 21 patients studied are shown in Table 1. Nine of these patients had previously been reported in less detail by Haygood *et al*. in 2012;[5] however, the other 12 had not been studied previously. The average age of the patients at the time of discovery of the first skeletal muscle metastasis was 58.1 years (range: 44–75 years). Only three of the patients were women and the rest were men. In 17 of the patients (81.0%), the histopathological subtype of the primary RCC was conventional clear cell RCC, with Fuhrman nuclear grades ranging from 2–4 (45.5% of the lesions were grade 3). There was one case of chromophobe RCC. In the remaining three patients, the primary tumours had been diagnosed at outside institutions and it was impossible to confirm the subtype of the original tumour.

Table 1: Demographic characteristics, outcomes and tumour conditions of skeletal muscle metastases as assessed by computed tomography imaging of renal cell carcinoma patients (N = 21)

Age* in years/ gender	Interval in months†	Outcome	Sites	Axial size in mm‡	Density without contrast§	Contrast enhancement¶
49/M	36	Died after nine months	Paraspinal	5 x 5	Isodense	Homogeneous
50/M	Presenting sign	Alive with minimal disease	Deltoid	40 x 37	Hypodense	N/A
47/M	2	Died after 46 months	*Pectoralis* major	14 x 8	Hypodense	Peripheral
			Paraspinal	11 x 8		Heterogeneous
			Paraspinal	2 x 2		Heterogeneous
			Gluteal	10 x 7		Heterogeneous
			Triceps	113 x 95		Heterogeneous
			Deltoid	13 x 11		Heterogeneous
62/M	28	Died after 46 months	Paraspinal	8 x 7	N/A	Homogeneous
44/M	3	Died after six months	Quadriceps	55 x 27	N/A	Heterogeneous
			Soleus	70 x 50	Heterogeneous	N/A
52/M	44	Died after 13 months	*Psoas*	47 x 35	Hypodense	Peripheral
54/M	8	Lost to follow-up	*Psoas*	14 x 14	N/A	Peripheral
			Paraspinal	14 x 9		Peripheral
			Gluteal	16 x 11		Homogeneous
			Gluteal	6 x 8		Homogeneous
			Supraspinatus	16 x 13		Peripheral
			Infraspinatus	25 x 14		Peripheral
61/M	58	Died after nine months	Paraspinal	16 x 13	Isodense	Peripheral
			Paraspinal	12 x 8		
73/M	14	Died after 52 months	Paraspinal	16 x 12	Isodense	Homogeneous
			Paraspinal	24 x 19	N/A	Isodense
			Latissimus dorsi	6 x 3	N/A	Homogeneous
			Gluteal	13 x 7	N/A	Homogeneous
			Gluteal	11 x 5	N/A	Lateral
			Supraspinitus	11 x 8	N/A	Homogeneous
			External oblique	12 x 7	Isodense	Peripheral
			Iliopsoas	9 x 9	N/A	Peripheral
66/M	31	Died after nine months	Gluteal	10 x 8	N/A	Homogeneous
			Gluteal	12 x 7		Peripheral
			Gluteal	12 x 10		Peripheral
			Paraspinal	7 x 6		Homogeneous
63/M	234	Died after 13 months	Paraspinal	11 x 8	Isodense	Homogeneous
71/M	6	Died after two months	*Psoas*	60 x 56	Isodense	Heterogeneous
66/F	12	Died after 37 months	Intercostal	27 x 24	Isodense	Peripheral
63/M	2	Died after four months	Gluteal	13 x 7	N/A	Homogeneous
75/F	31	Died after approximately 42 months or later	Gluteal	30 x 17	N/A	Peripheral
58/M	25	Alive with minimal disease after 65 months	*Psoas*	8 x 8	N/A	Peripheral
			Trapezius	14 x 11		Heterogeneous
			Latissimus dorsi	8 x 8		Homogeneous
			Intercostal	18 x 13		Heterogeneous
			Paraspinal	9 x 9		Peripheral
			Paraspinal	7 x 7		Peripheral
			Paraspinal	10 x 9		Peripheral
			Teres major	10 x 8		Heterogeneous

50/F	37	Died after 11 months	*Latissmus dorsi*	20 x 15	Isodense	Homogeneous
57/M	7	Died same month	Paraspinal	16 x 16	Isodense	Peripheral
			Paraspinal	7 x 7	Isodense	Peripheral
			Gluteal	15 x 9	N/A	Peripheral
			Psoas	14 x 9	Isodense	Peripheral
			Iliacus	13 x 13	N/A	Peripheral
			Teres major	13 x 14	N/A	Peripheral
62/M	6	Died after five months	*Psoas*	11 x 9	Isodense	Peripheral
44/M	75	Died after 33 months	Tongue	14 x 11	N/A	Peripheral
			Paraspinal	18 x 13	N/A	Heterogeneous
			Paraspinal	27 x 17	Isodense	Heterogeneous
			Paraspinal	22 x 17	Isodense	Peripheral
			Paraspinal	25 x 19	N/A	Heterogeneous
			Psoas	9 x 7	N/A	Heterogeneous
			Gluteal	25 x 24	N/A	Heterogeneous
			Gluteal	28 x 13	N/A	Heterogeneous
54/M	18[//]	Died after four months	*Infraspinatus*	26 x 22	N/A	Heterogeneous
			Paraspinal	8 x 6	Isodense	Homogeneous

M = male; F = female; N/A = not available.

**At the time the skeletal muscle metastases were first discovered or, if not reported, at the time the metastases first became visible on imaging. [†]Interval between the primary tumour and the discovery of the first skeletal muscle metastasis. [‡]Perpendicular measurements on the axial image in which the lesion appeared largest. Measurements were made using electronic callipers. [§]The surrounding muscle is the reference standard for computed tomography density. For some patients, there were no images available without contrast. [¶]One lesion was isodense to the muscle with contrast, so it is unclear whether it was enhanced. Heterogeneous enhancement means that the lesion was enhanced in a patchy fashion throughout its substance and not just around the periphery. [//]Interval between the primary tumour and when the muscle metastases were visible in retrospect.*

A total of 72 muscle metastases in this patient group were analysed, with smaller metastases in two patients with more than eight metastases excluded. Of these, 60 (83.3%) were in trunk muscles (including the *pectoralis* major), nine (12.5%) were in muscles of the upper extremities, two (2.8%) were in muscles of the lower extremities and one (1.4%) was in the tongue. Most of these metastases were asymptomatic and discovered via CT. Two patients complained of a painful swelling at the metastasis site and one reported a painless, palpable swelling. In one patient, the muscle metastasis was the initial presenting complaint.

The time interval between the discovery of the primary tumour and the discovery of the skeletal muscle metastases varied. Skeletal muscle metastasis was the presenting complaint for one patient and skeletal muscle metastases were omitted in radiological reports for another patient. Two patients had had RCC nine and 19 years before subsequently presenting with metastatic disease and a mass in the previously unaffected kidney. In the first of these latter two patients, the new renal mass was relatively large compared with the other masses and it was judged to be a new primary tumour. For the second patient, the new renal mass was distinctly smaller than several of the other masses, so it was judged to be a metastasis from the previous cancer. Including these four patients, and with the discovery of the originally unreported metastases considered to have occurred when they were identified on retrospective review, the interval between the discoveries of the primary tumour and the skeletal muscle metastasis ranged from 0–234 months (average interval: 32 months). Excluding these four patients, the interval between discoveries ranged from 2–75 months (average interval: 25 months).

Metastasis to the skeletal muscles was proven by direct biopsy in three patients. Among the remaining 18 patients, 13 had pathology-evidenced metastatic RCC in other locations and five had clinical and radiological evidence of metastasis to other organs typical of RCC. The mean size of the muscle metastases at the time they were reported (or when first visible, if not reported) was 18.3 mm in the greatest axial dimension (range: 2–113 mm). The average size of those that were asymptomatic at discovery was 16.3 mm.

A total of 39 lesions (54.2%) were oval [Figure 1], 16 (22.2%) were round, 15 (20.8%) were irregular and two (2.8%) were lobular. CT images without intravenous contrast were available for 29 lesions, nearly two-thirds of which (n = 19; 65.5%) were isodense to the adjacent muscle. Of 69 lesions with contrast-enhanced CT images, enhancement on post-contrast CT was homogeneous in 20 (29.0%), heterogeneous in 16 (23.2%) and peripheral in 33 (47.8%) [Figure 2]. Six patients had MRI examinations. All lesions with T2-weighted images demonstrated hyperintense signals. Five of the seven lesions with available T1-weighted pre-contrast images were hyperintense [Figure 3]. Although contrast enhancement was variable, all

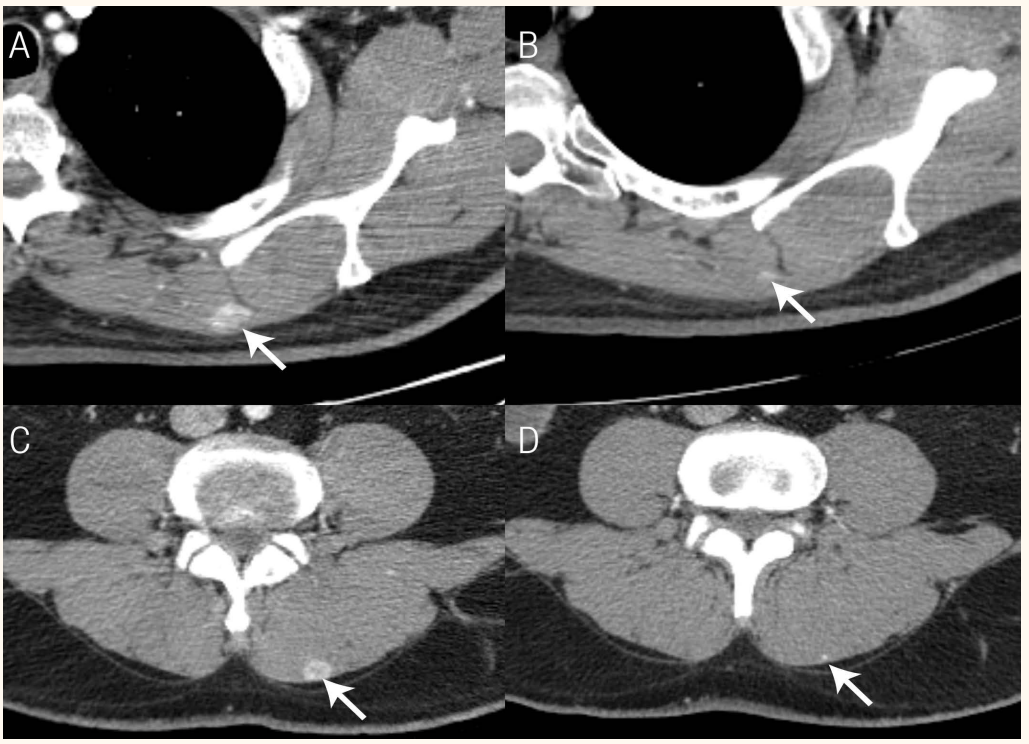

Figure 1A–D: Enhanced computed tomography (CT) images of a 58-year-old man with renal cell carcinoma. **A:** Initial detection and reporting of a left *trapezius* metastasis measuring 14 x 11 mm (arrow). **B:** The same metastasis was subtler and less well-defined yet still visible 11 months earlier (arrow). This lesion had a heterogeneous pattern of enhancement. **C:** Initial detection and reporting of a left paraspinal metastasis measuring 10 x 9 mm (arrow). **D:** The same metastasis was much smaller although still visible 11 months earlier (arrow). This lesion had a homogeneous pattern of enhancement when first visible which became peripheral later. Both muscle metastases appeared oval when they were first detected in cross-sectional imaging.

lesions showed enhancement. Small enhancing vessels feeding or draining the skeletal muscle metastases were noticed in five (7.2%) of the lesions for which contrast-enhanced CT was available [Figure 4]. Surrounding muscle oedema was seen in one case. No calcification was found in or around any of the lesions.

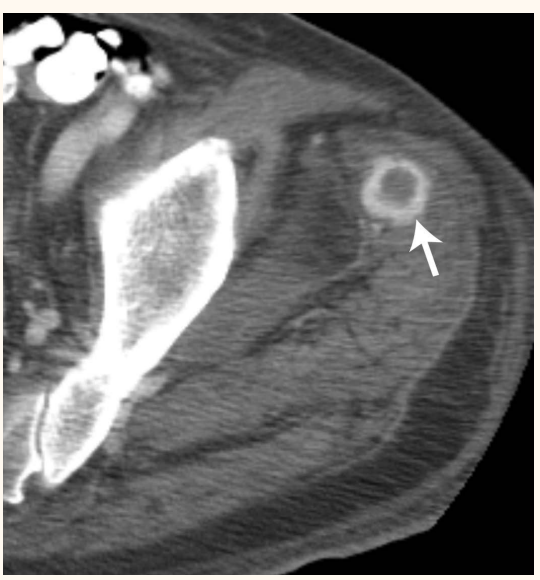

Figure 2: Contrast-enhanced computed tomography image of a man with renal cell carcinoma and left *gluteus medius* muscle metastasis showing peripheral contrast enhancement (arrow).

All but one of the patients with muscle metastases had metastases to other organs at the time the muscles metastases were discovered. These metastases occurred mainly in the lungs (85.7%), liver (28.6%), bones (33.3%) and brain (23.8%). The exception was the patient whose muscular metastasis was the presenting complaint; this patient was noted to have pulmonary nodules on a CT scan eight months after presentation.

Of the 20 patients for whom follow-up information was available, 18 have died to date. One patient, who presented with very advanced disease and metastases in multiple organs, died within one month of the discovery of the muscle metastases. The other 17 patients survived for between 2–52 months (average: 21 months). At the time of writing, two patients remained alive with minimal disease, one of whom had survived for more than five years after the discovery of the muscle metastases.

The literature review revealed 36 case reports detailing 37 cases of RCC metastasis to the skeletal muscles [Table 2].[2,3,7–40] There were 19 other patients reported in the literature; however, insufficient information was given regarding individual cases and

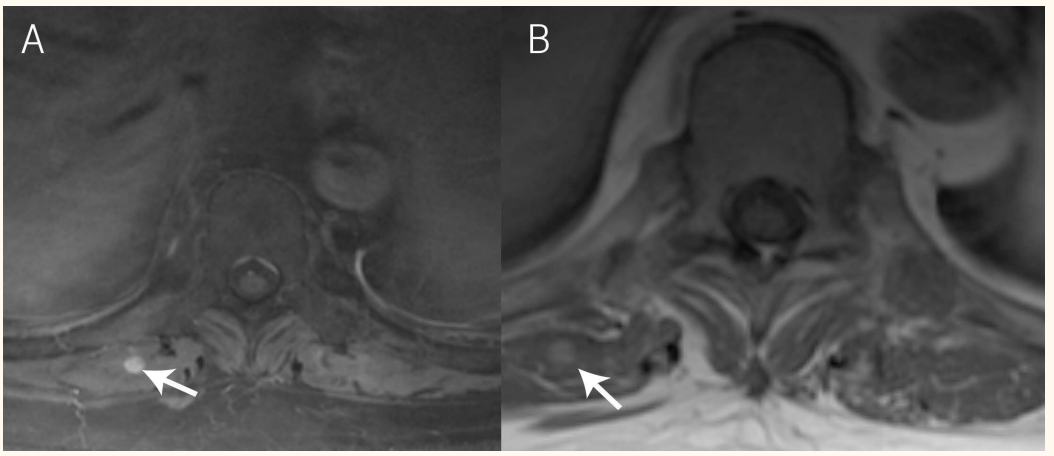

Figure 3A & B: Magnetic resonance imaging (MRI) of a 49-year-old man with renal cell carcinoma. **A:** Post-contrast fat-saturated T1-weighted axial MRI scan at the L2 level showing a small metastasis in the right paraspinal musculature that is enhanced brightly. **B:** Pre-contrast T1-weighted axial MRI scan at the same level shows that this small metastasis is hyperintense to the surrounding muscle (arrow).

these were therefore not included in the analysis.[4,8,9] The average age of the patients from the literature review at the time of the first skeletal muscle metastasis discovery was 61.9 years (range: 41–81 years). There were five women and 31 men. The age and gender of one patient was not specified.[34] In 18 (81.8%) of the 22 cases for which the histopathological subtype was available, the primary tumour was conventional clear cell RCC.[7,10,13,15,16,18,20–24,27,28,32,35,37,38,40] There was one case each of granular cell and sarcomatoid RCC.[31,39]

A total of 44 metastases in these 37 literature review cases were analysed, although the information available for each varied. Of the 43 lesions for which the location site was available, nine (20.9%) were in trunk muscles, 11 (25.6%) were in muscles of the upper extremities, 16 (37.2%) were in muscles of the lower extremities and seven (16.3%) were in muscles of the head and neck.[2,7–40] The majority of the skeletal muscle metastases in the literature were symptomatic. Only six patients had skeletal muscle metastases that were discovered incidentally on imaging.[7,16,18,23,29,37]

In seven reports, the muscle metastasis was the initial presenting complaint.[3,8,21,24,27,28,32] Skeletal muscle metastasis was found synchronously with the primary tumour in two cases.[29,37] There was no information regarding the time interval between the discovery of the primary tumour and discovery of the muscle metastasis in five cases.[9,11,26,34] For the remaining 23 cases, the interval ranged from 6–252 months (average: 101 months).[2,7,10,12–20,22,23,25,30,31,33,35,36,38–40] The average size of the skeletal muscle metastases at presentation, available for 28 of the lesions reported in the literature

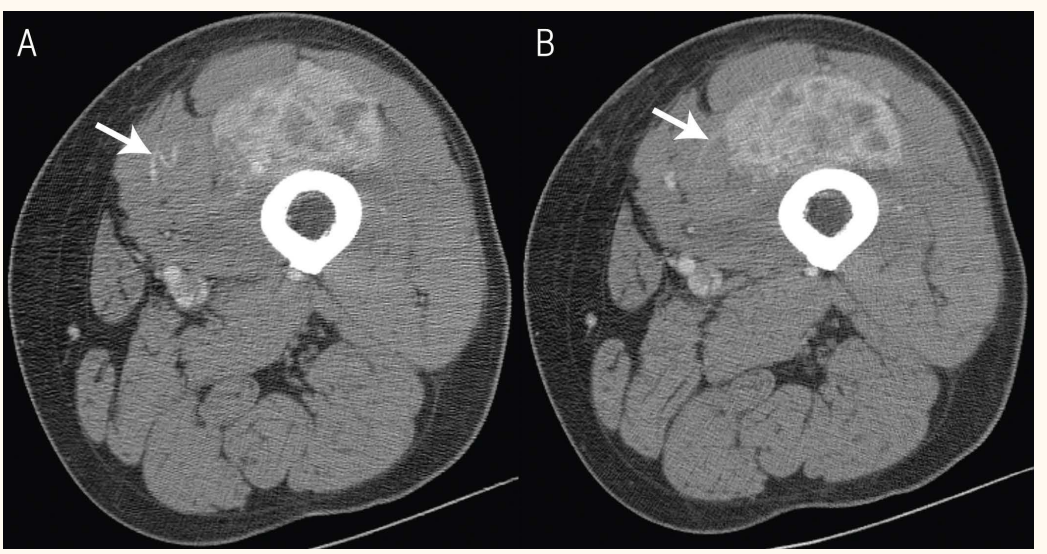

Figure 4A & B: Contrasted computed tomography images from a 44-year-old man with renal cell carcinoma showing muscle metastasis with visible feeding or draining vessels in the left quadriceps (arrows). This is also an example of a heterogeneous pattern of enhancement.

Table 2: Demographic characteristics, outcomes and tumour conditions of skeletal muscle metastases in selected renal cell carcinoma patients reported in the literature (N = 37)

Author and year of report	Cases	Age in years/gender	Interval in months[†]	Site	Size in mm
Chen *et al.*[2] 2005	1	50/M	168	*Vastus medialis*	50 x 40
Herring *et al.*[3] 1998	1	62/M	Presenting sign	N/A	N/A
Sakamoto *et al.*[7] 2007	1	65/M	72	Gluteal muscles	N/A
Capone *et al.*[8] 1990	1	63/M	Presenting sign	Extraocular muscles*	N/A
Pretorius *et al.*[9] 2000	1	73/F	N/A	Deltoid*	N/A
Nabeyama *et al.*[10] 2001	1	81/M	180	Triceps *brachii* *Brachioradialis*	40 x 30 10 x 10
Stener *et al.*[11] 1984	2	55/M	N/A	Hamstrings Adductor *magnus*	N/A N/A
		46/M	N/A	*Vastus medialis* *Vastus intermedius*	N/A N/A
Lee *et al.*[12] 2008	1	81/M	60	Thigh	50
Hur *et al.*[13] 2007	1	63/M	228	*Psoas* *Vastus medialis*	28 x 19 N/A
Pompo *et al.*[14] 2008	1	73/M	252	Biceps *femoris*	160 x 75
Nakagawa *et al.*[15] 1996	1	57/M	48	Masseter	10
Taira *et al.*[16] 2005	1	63/M	168	*Psoas*	15
Munk *et al.*[17] 1992	1	57/M	8	*Trapezius*	70 x 40
Linn *et al.*[18] 1996	1	58/M	168	*Psoas*	50
Judd *et al.*[19] 2000	1	72/F	60	Deltoid	100 x 80
Manzelli *et al.*[20] 2006	1	73/F	96	Quadriceps *Sartorius* Adductor *magnus*	90 x 50 35 30
Alexiou *et al.*[21] 1984	1	74/M	Presenting sign	Arm muscles	65 x 60
Alimonti *et al.*[22] 2003	1	62/M	6	Deltoid	30
Camnasio *et al.*[23] 2010	1	63/M	132	*Psoas*	18
Chandler *et al.*[24] 1979	1	62/M	Presenting sign	Biceps	100 x 80
Di Tonno *et al.*[25] 1993	1	55/M	144	Gluteal muscles	47
Egund *et al.*[26] 1981	1	60/F	N/A	Shoulder muscles	Large
Gal *et al.*[27] 1997	1	49/M	Presenting sign	Masseter	40 x 40
Gözen *et al.*[28] 2009	1	58/M	Presenting sign	*Gastrocnemius*	40 x 20
Hyodo *et al.*[29] 2009	1	65/M	Synchronous	*Infraspinatus*	N/A
Kang *et al.*[30] 2010	1	71/M	144	*Temporalis*	41
Karakousis *et al.*[31] 1981	1	63/M	69	Thigh muscles	N/A
Kishore *et al.*[32] 2006	1[‡]	42/M	Presenting sign	Shoulder muscles	80 x 70
Merimsky *et al.*[33] 1990	1	69/M	12	Biceps *femoris* Gluteal muscles	N/A
Peyster *et al.*[34] 1987	1	N/A	N/A	Extraocular muscles	N/A
Picchio *et al.*[35] 2010	1	58/M	60	Adductor *magnus*	50
Ruiz *et al.*[36] 1991	1	63/F	192	*Vastus lateralis*	N/A
Sano *et al.*[37] 2007	1	53/M	Synchronous	Paraspinal muscles	150

Schatteman *et al.*[38] 2002	1	69/M	24	*Trapezius*	60 x 30
Shibayama *et al.*[39] 1993	1	41/M	34	Tongue muscles	20
Yiotakis *et al.*[40] 2001	1	60/M	6	Masseter	15

M = male; N/A = not available; F = female.

**One large mass involving all of these muscles. †Interval between the primary tumour and the discovery of the first skeletal muscle metastasis. ‡Seven patients were not included in the analysis due to insufficient details.*

review, was 53.4 mm in the greatest dimension (range: 10–160 mm).[2,10,12–25,27,28,30,32,35,37–40]

Of the 14 metastases for which data on CT appearance were available, 10 showed enhancement and one was isodense to the muscle on non-contrasted CT.[7,9,12–18,23] Of the metastases for which data on MRI appearance were available, five had low to intermediate signal intensity and five had high signal intensity on T1-weighted images.[2,3,7,10,12,14,17,19,34,35] Two had intermediate signal intensity and nine had high signal intensity on T2-weighted images.[2,3,7,10,12,14,17,19,30,34,35] One was enhanced with contrast administration.[2]

Metastases in other organs—mainly the lungs and bones—were present at the time of or before the initial diagnosis of muscle metastasis in 17 of the 29 patients for whom this information was specified.[2,7,8,10,13,15,19,21,23,24,27,29,32,35,37–39] For 12 patients, the skeletal muscle metastasis was the only known metastasis at the time it was discovered.[16–18,20,22,25,28,30,31,33,36,40]

Discussion

The demographic characteristics of patients in both the study and literature review groups were relatively similar, with an average age of approximately 58 and 62 years, respectively. There were over six times more men than women, with a combined total of eight women (14.0%) and 49 men (86.0%). This marked male predominance was greater than would be expected with regards to population studies that have found a male-to-female ratio of less than 2:1 for cases of RCC.[1,41] Survival rates, which are probably similar to metastasis rates, also do not sufficiently differ between men and women with RCC to account for this male predominance.[1]

Presentation of skeletal metastases differed between the study group and cases from the literature review. The former group was distinctly more likely to have metastases in the trunk muscles (83.3%) and to have metastases discovered by staging studies when the lesions were asymptomatic and relatively small. These facts are probably related as metastases in deep muscles of the trunk (particularly the *psoas*) are not palpable until very large but do lie in the areas normally examined in CT scans of the chest, abdomen and pelvis. The sites of involvement among the study cohort predominantly involved the trunk muscles; this was similar to findings from other research.[5,42] Surov *et al.* studied a large group of patients with muscle metastases of all types.[43] They found a larger representation of metastases in the extremities and extraocular muscles, likely because the study included both patients from their own institution and those from previous publications.[43]

In contrast to the study group in the current study, patients in the literature review group were more likely to have metastases in the extremities (61.9%) and to have the lesions discovered due to symptoms. Furthermore, metastases were discovered when they were relatively large; metastases in this group were nearly three times larger in diameter on average than those in the study group. It is important to note that the apparent average size of metastases in the patients from the current study group would have been slightly elevated by the exclusion of smaller metastases in the two patients with more than eight metastases in total. It is possible that the pattern of metastasis location and size found among the study cohort was more typical of that expected in patients undergoing routine follow-up of known RCC, while case reports of RCC in the literature tend to describe unusual presentations of the condition.

The time interval between the diagnosis of the primary tumour and the detection of the muscle metastases varied greatly, with several very late appearances of metastases. Notably, the calculation of intervals in the study group was complicated by four patients (one patient presenting with skeletal muscle metastasis, one whose skeletal muscle metastases were omitted in radiological reports and two who had had RCC many years previously before presenting with metastatic disease). Many theories have been proposed to explain late recurrence of metastatic disease, including immunological and hormonal factors.[10] It is important that radiologists recognise that delayed skeletal muscle metastasis of RCC can occur so that early diagnosis and intervention are possible, particularly because the surgical excision of isolated metastases may improve disease-free survival.[11,44] In addition, recent developments in chemotherapy,

particularly the use of tyrosine kinase inhibitors, have made it possible to treat metastatic RCC, including skeletal muscle metastases, with reasonable chances of prolonging life.[45] To date, two of the patients in the study group, both of whom were treated with tyrosine kinase inhibitors, have continued to lead active lives years after the discovery of their skeletal muscle metastases.

Differentiating skeletal muscle metastases from other soft tissue tumours is important because of their different treatments and prognosis.[4,7] In many cases, a biopsy is needed to reach a definitive diagnosis, particularly for isolated lesions. Even when a patient has multiple metastases, this procedure can be useful to find muscle metastases. When several masses are present in patients with a known primary tumour, generally only one will need to be biopsied. The authors of the current study believe that masses in skeletal muscle are often fairly superficial and do not move during respiration; for these reasons, they may therefore be a good option for biopsy.

Slightly more than half of the patients in the literature review group had metastases in other organs before or at the time the skeletal muscle metastasis was discovered, while all but one of the patients in the study group had skeletal muscle metastases concomitant with metastasis in other organs. Damron *et al.* reported that RCC metastases in soft tissues, including skeletal muscle, almost always present as a solitary soft tissue mass after a variable period of time from the initial diagnosis of RCC.[46] Their view, however, was probably influenced by the fact that this type of metastatic RCC presentation is preferentially described among case reports in the literature as well as by the inclusion of their own cases of biopsy-proven metastases.[46] This inclusion criterion would favour isolated metastases because multiple metastases do not individually warrant a biopsy.

In general, skeletal muscle metastases are very subtle on non-contrasted CT (isoattenuating to the surrounding musculature) and can easily be missed in most cases.[12] After intravenous contrast administration, the most common pattern in the current study group was peripheral enhancement. Pretorius *et al.* found rim enhancement in 83% of skeletal muscle metastases and Surov *et al.* found peripheral enhancement in 32.5% of their cases.[6,9] In the current study, some of the patients' skeletal muscle metastases in the study group had heterogeneous and homogeneous patterns of enhancement with no obvious predominance of one over the other; this was similarly described in several other reports.[2,9,12–19] In contrast, Surov *et al.* found that the homogeneous pattern was the most common, with 52.5% of their cases exhibiting homogeneous enhancement.[6] In the current study, small feeding vessels to the skeletal muscle metastases were found in a few of the lesions among the study group. This feature has been described in previous reports using various imaging methods and has been theorised to be due to the production of lactic acid by tumours, which signals anoxia.[2,16,20] New vessels seek out the source of anoxia and provide vascularisation.[20,47]

The MRI signal intensity of the lesions in the study group was variable. It was not surprising that the signal intensity on T2-weighted images was generally higher than that of the surrounding muscle and that the lesions generally enhanced with contrast administration. Skeletal muscle metastases are usually reported to be hypo- to isointense to the muscle on T1-weighted images, with a small percentage sometimes being hyperintense.[12,48] Interestingly, however, 71% of the muscle metastases with pre-contrast T1-weighted images in the study group and 50% of those in the literature review group were hyperintense to surrounding muscle on T1-weighted images. It is important to note that none of the patients in the study group had a history of melanomas, which may be an explanation for the frequency of hyperintense T1 lesions among this cohort.

Certain limitations exist with regards to data reported from the current study, including the relative rarity of MRI studies for patients in the study group. Additionally, variable chemotherapy regimens were received by the patients, which prevented a meaningful study of the effects of specific drugs on the course of the disease and any muscle metastasis. Both CT and MRI scans were obtained over too long a stretch of time using different scan protocols and on various types of equipment to allow any meaningful analysis of specific imaging parameters. Finally, as this was a retrospective study of patients encountered in clinical practice and noted in teaching files, the sample was affected by selection bias. Despite this, 17 of the 21 patients presented during a time when information was being collected on all cases of skeletal muscle metastasis encountered. As a result, those patients comprised an essentially consecutive series. Another limitation of the current study was that the literature review did not identify or include every published case of RCC metastatic to skeletal muscle available as it was necessary to stop collecting data as of March 2013 and perform the analysis.

Conclusion

The possibility of skeletal muscle metastases should always be considered in patients with RCC, even long after primary treatment, so as to reduce the chance of

overlooking skeletal muscle metastases and improve staging. Skeletal muscle metastases from RCC may be invisible on CT without intravenous contrast, so contrast-enhanced studies are recommended for these patients. Metastases from RCC are often hyperintense to the surrounding muscle on T1-weighted MRIs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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