

## Foot metastasis: Current knowledge

Tommaso Greco,<sup>1,2</sup> Luigi Cianni,<sup>1,2</sup>

Domenico De Mauro,<sup>1,2</sup>

Giacomo Dughiero,<sup>2</sup> Maria Beatrice

Bocchi,<sup>1,2</sup> Gianpiero Cazzato,<sup>1,2,3</sup>

Giulia Ragonesi,<sup>2</sup> Francesco Liuzza,<sup>1</sup>

Giulio Maccauro,<sup>1,2</sup> Carlo Perisano<sup>1</sup>

<sup>1</sup>Fondazione Policlinico Universitario A. Gemelli IRCSS, Rome; <sup>2</sup>Università Cattolica Del Sacro Cuore, Rome; <sup>3</sup>Artrogruppo, Clinica San Feliciano, Roma, Italy

### Abstract

Foot metastasis are rare and often overlooked due to non-specific symptoms. This often leads to misdiagnosis delaying the right diagnosis. Metastatic disease of the foot is rare. Foot pain and swelling may be the presenting symptom of an occult malignancy. If metastatic disease is not kept in the differential diagnosis of foot pain, diagnosis and treatment will be delayed. The purpose of this study was to analyze articles presenting cases of foot metastasis to provide a more accurate incidence of symptomatic foot acrometastasis as well as to review the clinical course and outcomes. Studies were searched on PubMed/Medline from the inception to February 2020. All studies included in the review presented foot metastasis either with or without a known primary tumor. Most of the articles were case reports, to which we added two case reports of foot acrometastasis produced by our Institute. Forty-three studies with a total of 45 patients were included in this review. The literature published mostly concerning case reports about old patients (average age: 63,2), in a late phase of their disease. Lung cancer appeared to be the most common primary tumor, followed by endometrial and breast cancer. In the 36% of the cases foot metastasis were found when the primary site was still unknown. Calcaneus and metatarsal bones were the most common bones involved. Surgical solution is rare, the chosen treatments are often of palliative care. Prognosis was often poor, death occurred within 2 years since the discovery of foot metastasis in about 50% of cases.

### Introduction

Foot metastasis are a very rare occurrence in patients with an oncological

history. Studies suggest that only the 0.007-0.3% of cancer patients develops acrometastasis<sup>1</sup>- metastasis to hands and feet - and among those, less than 50% involves feet.<sup>2</sup> Therefore, these outbreaks are often underdiagnosed or misdiagnosed with a significative delay of the diagnosis, leading to several inappropriate treatments. This is the main reasons why foot metastasis have such a poor prognosis, in association with the fact that acrometastasis usually occur only after a widespread dissemination of the tumor.<sup>1</sup> The tumor histotype is mainly lung cancer, followed by gastrointestinal-tract and genito-urinary tract tumours.<sup>3</sup> Associated signs and symptoms are generally non-specific and can be identified with soft tissue swelling, functional impairment and intermittent pain.<sup>4</sup> Metastasis diagnosis is often not considered at first because of the great account given to differential diagnoses, mostly associated to benign conditions such as gout, rheumatoid arthritis, ligamentous sprains, osteoarthritis or even Paget's disease.<sup>5</sup> Furthermore, estimates of foot acrometastasis are probably low owing to the common practice of excluding the distal extremities from metastatic skeletal surveys or whole-body computed tomography.<sup>6</sup> There is a wide variety of treatments, from pharmacological therapy to External Beam Radiation Therapy (EBRT) and Surgery. These kinds of treatments have often a palliative aim, to grant a better quality of life.

### Materials and Methods

A literature review using the PubMed/Medline database was performed (from the beginning to February 2020). The search strategies (using a combination of controlled vocabulary and text word terms) were: foot metastasis OR calcaneal metastasis OR calcaneus metastasis OR talus metastasis OR navicular metastasis foot OR cuboid metastasis OR cuneiform metastasis OR metatarsal metastasis OR phalanx metastasis foot OR hindfoot metastasis OR forefoot metastasis OR midfoot metastasis OR soft tissue metastasis foot. Our research initially produced 221 articles, to which we added two case reports our Institute produced respectively in 2006<sup>7</sup> and in 2019.<sup>8</sup> Studies in our review include both ones where foot acrometastasis were secondary to a known primary tumor, and ones where they were the first manifestation of a still unknown tumor, for which diagnosis was made afterwards. All duplicates, articles without full text and studies regarding primary tumors of the bone or soft tissue of the foot were excluded. Two review authors

Correspondence: Tommaso Greco, Università Cattolica del Sacro Cuore, Largo Francesco Vito, 1, 00168 Rome, Italy.

Tel. : +39 3807582118

E-mail: tommasogreco.rm@tiscali.it

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independently selected eligible articles. Disagreements at any stage were resolved by consensus or a third party adjudication. Descriptive statistics was used to summarize the data. All the outcomes reported by each study were analyzed and when possible, data were pooled to generate frequency-weighted values to summarize outcomes.

### Results

Following the PRISMA flow-chart (Figure 1),<sup>9</sup> 44 studies were finally included in the review (Table 1).<sup>7,8,10-51</sup>

In this review we gathered 46 different cases of patients with foot metastasis, including 25 females (54,4%) and 21 males (45,6) with an average age of 63,2 (±18,0) years old (Table 2). Thirty seven percent of patients presented acrometastasis as first manifestation of disease. The most common locations of primary tumors in patients with a positive history of neoplastic disease were the lung in 28,3% of cases, followed by endometrium (17,4%) and breast cancer (10,9%). Subsequently, we discuss the main features of the principle types of foot metastasis found in our review.<sup>7,8,10-51</sup>

**Table 1. Patient demographics, diagnostic imaging and survival.**

Author	Year	N° of case	Sex	Age	Primary Site	Metastatic Site	Diagnostic Imaging	Survival (months)
Cooper <sup>10</sup>	1994	1	F	59	Occult - Endometrium	Right calcaneus	X-ray, BS	60
Kemnitz <sup>11</sup>	1996	1	M	68	Occult - Lung	Left 1° MT	X-ray	5
Groves <sup>12</sup>	1998	1	F	58	Breast	Left calcaneus	X-ray, MR, CT, BS	
Parikh <sup>13</sup>	1998	1	M	1	Kidney	Right heel soft tissue lesion	CT, X-ray, BS	18
Delgado <sup>14</sup>	1998	1	F	42	Occult - Lung	Right 3° MT	X-ray, BS, MR	
McGarry <sup>15</sup>	2000	1	M	45	Occult - Lung	Right calcaneus	MR	21
Kaufmann <sup>16</sup>	2001	1	F	88	Lung	Right calcaneus	X-ray, BS	
Oh <sup>17</sup>	2002	1	M	82	Prostate	Right cuboid	BS, X-ray, MR	
Manolitsas <sup>18</sup>	2002	1	F	76	Occult - Endometrium	Right calcaneus	X-ray, BS	11
Yadav <sup>19</sup>	2004	1	M	55	Occult - Kidney	Right 2° MT	X-ray	
Osterhouse <sup>20</sup>	2004	1	F	80	Breast	Distal left and right tibia and fibula, left calcaneus	Bilateral X-ray	
Kouvaris <sup>21</sup>	2005	1	F	59	Breast	Left talus	X-ray, MR, BS	18
Amiot <sup>22</sup>	2005	1	F	86	Endometrium	Left hallux distal phalanx	X-ray	
Maccauro <sup>7</sup>	2006	1	F	64	Occult - Kidney	Left talus	X-ray, MRI, BS	
Duarte <sup>23</sup>	2007	1	M	61	Lung	Left 3° MT	X-ray, BS, MR	
Plaza <sup>24</sup>	2008	1	F	82	Melanoma	Foot dorsum soft tissue		
Allman <sup>25</sup>	2008	1	M	91	Waldenstrom Macroglobulinemia (NH lymphoma)	Right hallux distal phalanx and left cuboid	X-ray, BS, MR, PET	
Agrawal <sup>26</sup>	2008	1	M	74	Prostate	Left calcaneus and cuboid	BS, X-ray	
Biyi <sup>27</sup>	2009	1	F	37	Breast	Right 2° MT	X-ray, CT, BS	18
Pichi <sup>28</sup>	2009	1	M	60	Buccal Mucosa	Left talus	CT, PET	24
Ellington <sup>29</sup>	2009	1	M	48	Colon	Left cuboid	X-ray, MR, CT, BS	8
		1	F	70	Rectum and lung	Right calcaneus	X-ray, MR	10
		1	M	84	Colon	Right foot soft tissue and 3° MT	X-ray, MRI, PET-CT	13
Dutta <sup>30</sup>	2011	1	M	53	Esophagus	Right V° MT	X-ray, BS	
Choufani <sup>31</sup>	2011	1	M	58	Occult - Kidney	Right foot medial and middle cuneiform	X-ray, CT	
Iselin <sup>32</sup>	2011	1	M	62	Occult - Lung	Navicular bone	X ray, CT, MR, BS	12
Pieters <sup>33</sup>	2011	1	F	76	Endometrium	Left sinus tarsi and calcaneus	X-ray, MR	36
Wijayaratna <sup>34</sup>	2013	1	F	88	Occult - Colon-rectum	Left 1° MT	MR, PET	
Ryder <sup>35</sup>	2013	1	F	82	Occult - Urothelial of the ureter	Left calcaneus	X-ray, MR, BS, CT	21
Samuelian <sup>36</sup>	2013	1	M	52	Pharynx	Right foot soft tissue	CT, PET-CT, US, X-ray	9
Dai <sup>37</sup>	2014	1	F	58	Occult - Lung	Left calcaneus	X-ray, CT, MR, BS	6
Rice <sup>38</sup>	2014	1	F	86	Endometrium	Left calcaneus	X-ray, MR, PET-CT	1
Kaynak <sup>39</sup>	2014	1	M	55	Lung	Left talus	MRI, BS	4
Rice <sup>40</sup>	2015	1	F	82	Lung	Right talus	X-ray	1
Reyes <sup>41</sup>	2015	1	M	64	Prostate	Left navicular	BS, CT, MRI, WBC scan, X-ray	
Longo <sup>42</sup>	2015	1	F	62	Occult - Endometrium	Left 5° MT	X-ray, CT, MR	
Kumar <sup>43</sup>	2015	1	F	54	Urothelial of the bladder	Left 1°, 2° and 3° MT	MR, X-ray, PET	
Jaffe <sup>44</sup>	2016	1	F	56	Breast	Left talus and soft tissue	X-ray, MR, BS	
Singh <sup>45</sup>	2016	1	F	63	Occult - Lung	Left calcaneus	MR, BS, CT, FDG-PET	
Li <sup>46</sup>	2016	1	M	61	Occult - Lung	Left cuneiform	BS, SPECT/CT	
Gan <sup>47</sup>	2017	1	M	66	Occult - Lung	Left talus	X ray, CT, MRI	
Tonogai <sup>48</sup>	2018	1	M	59	Kidney	Left calcaneus	X-ray, CT, MRI	
Martin <sup>49</sup>	2018	1	M	71	Lung	Right talus		
Nasi <sup>50</sup>	2018	1	F	14	Chest wall Ewing's sarcoma	Left talus	PET, CT, BS, MR	
Madabhavi <sup>51</sup>	2019	1	F	66	Occult - Endometrium	Multiple right tarsal bones	X-ray, BS	
Perisano <sup>8</sup>	2019	1	F	50	Endometrium	Left cuboid, IV-V MT	US, X-ray, PET-CT	8

MT Metatars; BS Bone Scan; MR Magnetic Resonance; US Ultrasonography; PET Positron Emission Tomography.

### Lung Cancer

Among the foot metastasis taken into account, the largest number of them takes origin from lung cancer. This reflects both the prevalence of lung carcinoma and its predilection for the skeleton in metastatic spread.<sup>52</sup> These kinds of lesion in more than half of cases represent the first occurrence, even before the diagnosis of the primary tumor. Commonly, the localization is at the hindfoot (talus and calcaneus), and rarely metastasis involve 2 or more bones of the foot. The chances of survival after the diagnosis of foot metastasis are very low, indeed the majority of the patients dies in few months.<sup>11,15,29,32,37,39,40</sup>

### Gynaecological and Breast Cancer

Gynaecological cancers are well described, with 8 cases referring about foot metastasis. Within “women’s cancers” - breast and uterus - endometrial carcinoma is the first primary tumor related to this kind of metastasis in this group, strictly followed by breast cancer. Foot metastasis in gynaecological cancers often occur on the calcaneus and are characterized by lesions which are mostly lytic.<sup>18,22</sup> Carcinoma of the uterus and Breast cancer differ in timing of diagnosis of the primary lesion: foot metastasis are often the first occurrence to be noticed in patients affected by endometrial cancer.<sup>10,18,42,51</sup> Breast cancer, instead, is already diagnosed at the time of foot metastasis discovery.<sup>12,20,21,27,44</sup>

### Genito-urinary Cancer

Genito-urinary cancer usually involves bones in metastatic dissemination. Kidney and prostate tumors are the most related to foot metastasis, but the kind of lesions they determine are not the same: renal cancer, is usually linked to the occurrence of lytic lesions,<sup>7,19,31,48</sup> as it happens to most of other tumors. Bone metastasis from prostate cancer, instead, are osteoblastic, sclerotic lesions.<sup>17,26</sup> Multiple foot bone lesions are not rare.<sup>26,31</sup> Moreover, two articles described cases of tumors of urothelial origin (one of the urether and one of the bladder

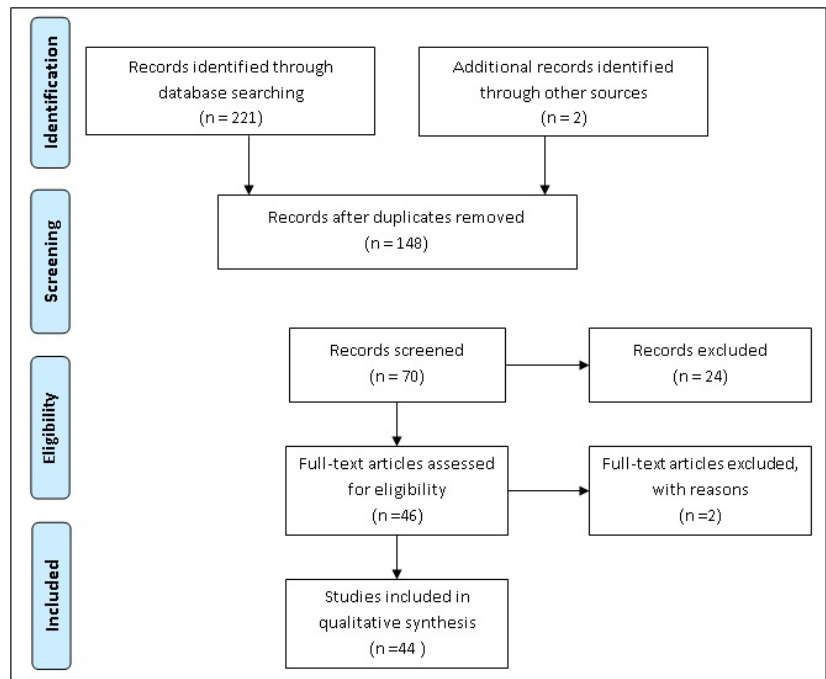
**Table 3. Localization of foot acrometastasis.**

Hindfoot	Total	(23)
	Calcaneus	14
	Talus	9
Midfoot	Total	(9)
	Cuboid	5
	Navicular	2
	Cuneiforms	2
Forefoot	Total	(13)
	Metatarsal bone	11
	Phalanx	2
Soft tissue	Total	5

**Table 2. Patient demographics, type of tumor, biopsy and treatment.**

Total Case		45
Sex	F	25 (53,3%)
	M	21 (46,7%)
Average age		63,2 ± 18,0
Type of tumor	Lung	13/46 (28,3%)
	Endometrium	8/46 (17,4%)
	Breast	5/46 (10,9%)
	Kidney	5/46 (10,9%)
	Colon-rectum	4/46 (8,7%)
	Prostate	3/46 (6,5%)
	Urinary tract	2/46 (4,3%)
	Single case (Esophagus, Melanoma, W. Macroglubulinemia, Pharynx, Buccal Mucosa, Chest wall Ewing's sarcom)	6/46
	Primry Occult	Yes
	No	29/46 (63%)
Biopsy	Total	41/45 (91,1%)
	Open biopsy	17/41 (41,5%)
	FNA	15/41 (36,6%)
	Aspiration of sinovial fluid	1/41 (2,4%)
	Not specified type of biopsy	8/41 (19,5%)
Treatment	Refused	1
	Radiotherapy (alone or with surgery)	27
	Surgery	17
	Not specified	4
Survival (months)	Average	15,2 ± 13,6
	Range	1-60

FNA, Fine needle aspiration.



**Figure 1. PRISMA flow-chart.**

urothelium) giving rise to foot acrometastasis.<sup>35,43</sup>

### Gastrointestinal-Tract Cancer

Gastrointestinal-tract cancer is also related to foot metastasis, but reported cases are much less than the aforementioned ones. Colo-rectal cancer is the most common one. Secondary foot lesions occurring in these cases are usually lytic lesions diagnosed during primary tumor follow-up. Thus, foot metastasis are linked to a worst prognosis. Most of the patients died within a year since the foot metastasis diagnosis. Our review also included a single case of metatarsal metastatic bone lesion originating from esophageal cancer.<sup>30</sup>

### Others

Single cases of foot metastasis are reported in patients with Waldenström Macroglobulinemia,<sup>25</sup> Ewing's Sarcoma,<sup>50</sup> Melanoma,<sup>24</sup> Pharynx<sup>36</sup> and Buccal Mucosa.<sup>28</sup> In each of them, the primary tumor was already diagnosed at the time foot metastasis was discovered.

## Discussion

### Symptoms

The onset of the symptoms in foot metastasis is generally non-specific and can be identified with soft tissue swelling, erythema, functional impairment and intermittent pain. Usually this leads to a misdiagnosis, the most common foot problems come up in differential diagnosis such as heel spur, plantar fasciitis, Haglund's syndrome, etc. Therefore, before the correct diagnosis was found, patients went under different and unnecessary treatments, like simple analgesia or orthotics (5 patients).<sup>10,12,14,18,37</sup>

### Diagnostic Investigation

The diagnostic process was more or less the same for each patient, starting from an X-ray examination in 80% of cases. Among the 46 cases we have taken into account, only in 9 cases patients did not undergo X-Ray examination. MRI and CT, together with bone scan, are the most commonly examinations used by physician in these cases, both looking for the primary tumor (in 17 cases foot metastasis were diagnosed before finding the primary tumor) and analyzing the foot lesion itself. During a deeper investigation 19 patients showed other metastasis in different body districts (bone and/or parenchymatous). Forty-one of the 45 patients (91,1%) who accepted the treatment underwent a biopsy for histological confirmation and definitive diagnosis. Among these, 17 patients

underwent an open biopsy.<sup>8,10,11,13,14,23,28,31,32,36-38,40,44,45,47</sup>

### Localization

The hindfoot was a common metastatic site (Calcaneus and Talus), with 23 occurrences (Table 3), followed by the forefoot and midfoot (13 and 9 localizations, respectively). Among single bones, 14 patients had findings at the Calcaneus,<sup>10,12,15,16,18,20,26,29,33,35,37,38,45,48</sup> 9 at the Talus<sup>7,21,28,39,40,44,47,49,50</sup> and 5 at the Cuboid.<sup>8,17,25,26,29</sup> Eleven patients had metastasis at metatarsal bones.<sup>8,11,14,19,23,27,29,30,34,42,43</sup>

### Treatment and Prognosis

Treatment options are numerous and various, from simple palliative care (5 patients) to surgical intervention. Only one patient refused every kind of therapy.

The treatment was rarely surgical, most of the patients were not eligible for a surgical approach, only 17 of 44 patients were taken to the operating room. No surgical choices were clearly prominent, 6 patients underwent simple curettage, 6 others had an excision of the metastatic lesion, and only 5 of them had a more radical surgery (disarticulation/amputation or wide resection). Despite surgical intervention, the prognosis remained poor.<sup>13,28,29,37</sup>

Radiotherapy on the metastasis site, whether alone or pre/post-surgery, was delivered to 27 out of 44 patients, often with palliative purposes.<sup>7,8,12,14-19,21,25-27,31,34-36,42,45,49,50</sup> Systemic therapies, such as chemotherapy, hormonal therapy and biological drugs, were also given to reach a better prognosis for both primary and secondary lesions. Five patients only had palliative care. Most of them had a poor prognosis.

We found prognosis information for 20 out of 46 cases. Eighteen of them died within 2 years, more than half of them within 1 year (10 patients).<sup>8,11,18,29,32,36-40</sup>

## Conclusions

Metastatic tumors of the foot present special challenges in diagnosis and management, and are usually found in widespread cancer disease. Interestingly, in our series a wide variety of tumors is able to metastasize to the foot and highlighting that most primary cancers should be considered as having the potential to metastasize to the foot. In a meaningful number of cases, foot acrometastasis are the first sign of disease. Thirty seven percent of cases from our review presented acrometastasis as the first sign of malignancy. This is an interesting

finding since, in past literature, acrometastasis as first presentation of occult malignancies was estimated to be around 10%.<sup>53</sup> Foot metastasis have likely become more frequent throughout the years, both because neoplastic patients tend to live longer and clinicians probably are more aware of the malignant potential of foot lesions. The finding of foot metastasis is indicative of an already advanced disease and a poor prognosis. Average survival in our review was 15,2 months ( $\pm$  13,63) similarly with the literature.<sup>5,6</sup> Patients often presented with a history of swelling, pain, functional impairment, skin changes, ulcers, lesions and sometimes drainage. This underlines the importance of a thorough history taking and physical examination in patients with these symptoms and especially in those with a known history of cancer. These lesions are often misdiagnosed as other more common pathologies (i.e. infections, gout, etc.) and do not improve with standard treatment for the aforementioned conditions. It has been reported that the diagnosis of an osseous metastasis of the foot is often delayed for between 1 and 24 months.<sup>5,6</sup> However, plain radiographs, bone scan, MRI, CT, and biopsy usually reveal the underlying diagnosis. Since foot metastasis are very rarely observed, there is no standard protocol for treatment; treatment should be tailored to the single patient according to individual needs and life expectancy. Therapeutic management should be assigned to a multidisciplinary team made by oncologists, orthopedic surgeons, radiotherapists and, if necessary, vascular and plastic surgeons. Because of the poor prognosis, treatment is aimed at palliation: goals should be to control local symptoms and preserve function.<sup>54</sup>

Treatment, which depends on the patient's prognosis, may consist of cast immobilization, bracing, narcotics, anti-inflammatories, surgical amputation, local resection with or without augment, systemic chemotherapy, and local radiation.

Definitive surgical intervention can be planned if the patient is a surgical candidate. In addition, patients may elect for non-operative treatment based on their projected lifespan. However, reconstruction or amputation may improve a patient's remaining quality of life. The decision between reconstruction and amputation is complex, requiring a discussion with the patient on a case-by-case basis. Reconstructive efforts should be aimed not only to preserve the limb but also to avoid creating local or distant metastasis.

When facing a patient older than 40 years old presenting with a foot lesion, the

chances of it being malignant should always be kept in mind to avoid delaying diagnosis and treatment, which could improve pain control and quality of life and increase the chances of preserving the involved limb. Foot metastasis must always be included in the differential diagnosis when the clinical picture raises suspicion.

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