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Dermatoscopic patterns of cutaneous metastases: A multicentre cross-sectional study of the International Dermoscopy Society

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ETHICS STATEMENT

The patients in this manuscript have given written informed consent to the publication of their case details. The study titled 'DERMATOSCOPIC PATTERNS OF CUTANEOUS METASTASES: A MULTICENTER CROSS-SECTIONAL STUDY OF THE INTERNATIONAL DERMOSCOPY SOCIETY' was approved by Ethics scientific committee of University Clinical Center of Nis number 38788/2.

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Abstract

Background: The detection of cutaneous metastases (CMs) from various primary tumours represents a diagnostic challenge.

Objectives: Our aim was to evaluate the general characteristics and dermatoscopic features of CMs from different primary tumours.

Methods: Retrospective, multicentre, descriptive, cross-sectional study of biopsy-proven CMs.

Results: We included 583 patients (247 females, median age: 64 years, 25%–75% percentiles: 54–74 years) with 632 CMs, of which 52.2% (n = 330) were local, and 26.7% (n = 169) were distant. The most common primary tumours were melanomas (n = 474) and breast cancer (n = 59). Most non-melanoma CMs were non-pigmented (n = 151, 95.6%). Of 169 distant metastases, 54 (32.0%) appeared on the head and neck region. On dermatoscopy, pigmented melanoma metastases were frequently structureless blue (63.6%, n = 201), while amelanotic metastases were typified by linear serpentine vessels and a white structureless pattern. No significant difference was found between amelanotic melanoma metastases and CMs of other primary tumours.

Conclusions: The head and neck area is a common site for distant CMs. Our study confirms that most pigmented melanoma metastasis are structureless blue on dermatoscopy and may mimic blue nevi. Amelanotic metastases are typified by linear serpentine vessels and a white structureless pattern, regardless of the primary tumour.

INTRODUCTION

Identifying cutaneous metastases (CMs), which can originate from a wide range of primary tumours, presents a significant diagnostic challenge. In autopsy studies involving cancer patients, the incidence rate of CMs varies widely, ranging from as low as 0.2% to as high as 9%.[1–7] These metastases may emerge either concurrently or at varying time intervals in relation to the diagnosis of the primary tumour. In some cases, the appearance of CMs may even serve as the first indication of an undiagnosed malignancy.[1,2,5–7]

The differential diagnosis of CMs is complex and spans a broad array of conditions, including adnexal tumours, cysts, basal cell carcinoma, primary melanoma and other types of both malignant and benign skin proliferations.[5–9] Knowledge of the varied morphologies of these lesions is essential for effective diagnosis. While dermatoscopy has proven valuable

in diagnosing a wide variety of skin lesions, both pigmented and non-pigmented, limited data exist on its efficacy in diagnosing skin metastases.[8–12]

Furthermore, detailed descriptions of dermatoscopic patterns associated with CMs from different primary malignancies are notably lacking. One potential explanation for this gap in knowledge could be that skin metastases, excluding those from melanoma and other skin cancers, are rarely encountered by dermatologists. Medical specialties such as oncology lack extensive experience in utilizing dermatoscopy for diagnosis. Given the considerable impact that CMs can have on a patient's prognosis and treatment strategy, timely and accurate identification of these metastases is crucial.

Our objective was to collect a large dataset of CM cases and to describe the general characteristics and dermatoscopic patterns associated with CMs stemming from different primary tumours.

METHODS

Our research was a retrospective, multicentre, cross-sectional study initiated by the International Dermoscopy Society (IDS). We solicited high-resolution dermatoscopic images of CMs from contributing centres, along with optional clinical photographs and supplemental data, such as age, sex, anatomical location of both primary tumours and CMs, and histopathological diagnoses. Ultimately, we collected a dataset comprising 632 histopathologically-confirmed CMs involving 581 patients. These cases were sourced from distinct participating centres across multiple countries, including Austria, Italy, Serbia, Spain, Greece, France, Germany, Australia, Japan, the USA, Argentina, Belgium, Poland, Sweden, Croatia, Israel, North Macedonia, Brazil, Romania and Turkey. The 632 CMs were categorized into three distinct groups, as outlined in Table 1. Cutaneous melanoma metastases were further classified as either locoregional—occurring between the primary melanoma site and regional lymph node—or distant, appearing beyond the regional lymph node. CMs emanating from other malignant neoplasms were designated as distant if they were situated in anatomical regions disparate from the primary tumour. For breast cancer cases, distant CMs were defined as those not localized to the affected breast.

For the purposes of our analysis, we generally utilized only a single image per patient, even when multiple CMs were present. Exceptions were made when the dermatoscopic appearances of the CMs exhibited morphological differences, warranting multiple case inclusions in the study. Dermatoscopic images with insufficient resolution or image quality, as well as cases lacking a definitive histopathological diagnosis, were excluded from the study.

Two experienced dermatologists (D.T and J.S.F) independently evaluated the dermatoscopic images of CMs, operating without prior knowledge of the histopathological diagnoses. The two readers focused on several criteria, including pigmentation (pigmented or non-pigmented), colour variations (black, brown, blue, grey, red, white, yellow, orange, purple), dermatoscopic patterns (reticular, dots/clods, radial lines, structureless), and the presence and distribution of vessels. Additional dermatoscopic features like regression, ulceration/

erosion and white lines were also considered. Subsequently, we calculated the interobserver agreement between the two dermatologists and opted to exclude the feature ‘white lines’ from further analysis due to poor interobserver agreement.

Statistical analysis

Continuous variables are reported as median and 25% and 75% percentiles. *T*-tests or Mann–Whitney tests were used for the comparisons of continuous variables, and chi-square tests or the Fisher exact test for proportions. A p-value < 0.05 was considered statistically significant.

RESULTS

General data

We collected data on 632 histologically confirmed CMs of 583 patients including 247 females (42.4%) and 332 males (56.9%). Four cases had unreported sex. The patients had a median age of 64 years (25%–75% percentiles: 54–74 years). Table 1 provides a detailed breakdown of the types of primary tumour and their categorization for subsequent analyses. Melanoma was the most prevalent malignant neoplasm associated with CMs in our series, followed by breast cancer and gastrointestinal tract (GIT) cancer. The latter category included tumours of the pharynx, oesophagus, stomach, small intestine, large intestine, rectum and anus. Of the 632 CMs, 330 (52.2%) manifested as locoregional, and 169 (26.7%) were categorized as distant metastases. Data on location were missing for 133 (21.1%) CMs. Among the 474 melanoma metastases, 260 were locoregional, 56 were distant, and location information was missing in 128 cases. Distant melanoma metastases most commonly appeared in the head and neck region. For distant CMs related to breast, lung, GIT and renal cancers, the trunk and head and neck regions were more commonly involved than other anatomical sites (Table 2).

Dermatoscopic findings

Of the 632 CMs, 323 (51.1%) were pigmented, whereas 309 (48.9%) were non-pigmented. The majority of the 323 pigmented CMs were melanoma metastases (n = 316). Vessels were noted in 289 (45.7%) of non-pigmented CMs and 132 (20.8%) of pigmented CMs. In dermatoscopic evaluations, prominent vessels were observed in all lung cancer metastases and in 96.6% of breast cancer metastases. Linear serpentine vessels were the most commonly observed type of vessels, present in 56.3% of all CMs. Ulceration was detected in 11.1% of metastases, with squamous cell carcinoma (31.2%), GIT (24%) and lung CMs (23.8%) exhibiting the highest frequencies. Among pigmented melanoma metastases, structureless blue was the dominant pattern, occurring in 63.6% of cases (Figure 1). Structureless brown and structureless white patterns were also common, appearing in 57.2% and 68.6% of cases, respectively. Structureless white was the most prevalent pattern overall, identified in 84.2% of all CMs (n = 532). Irrespective of their primary origin, non-pigmented CMs most commonly displayed a combination of linear serpentine vessels and a structureless white pattern (Table 3) (Figure 2).

DISCUSSION

Despite advancements in dermatoscopy, data on distinguishing CMs from other skin lesions remain scant. Studies suggest that up to 10% of metastatic cancer patients exhibit CMs, with melanoma being the most frequent culprit, followed by breast and upper respiratory tract cancers.[1,2,7,11–13] As expected, our study found melanoma CMs to be most prevalent, succeeded by breast, GIT and lung CMs.

Melanoma CMs often manifest subtly, resembling other benign or malignant skin lesions such as nevi, haemangiomas, cysts, primary melanoma and basal cell carcinoma.[8–14] Accurate diagnosis is essential for effective treatment and staging, especially since the American Joint Committee on Cancer has incorporated CMs into the new TNM classification for cutaneous melanoma.[15] Melanoma metastases can emerge either near the original tumour (locoregional) or at distant sites.[10–14] In our study, distant CMs were not rare, making up 26.7% of all cases. This high prevalence may be influenced by our case selection methods. Our study contributes to the sparse existing literature by identifying prevalent dermatoscopic patterns in melanoma CMs. The majority of melanoma CMs were pigmented, with structureless blue and brown patterns being most common. The key differential diagnosis for pigmented melanoma CMs is blue nevi, which also frequently appear in the head and neck region. In clinical practice, the presence of vascular structures on dermatoscopy, a known history of melanoma and recent onset can help differentiate isolated melanoma CMs from blue nevi. We also demonstrated that non-pigmented melanoma metastases are indistinguishable from other non-pigmented CMs.

Few studies have concurrently examined CMs across various cancers.[1–5] Our research reveals a high frequency of distant CMs localized on the trunk and head and neck regions. Other studies reported varying results, highlighting the need for region-specific surveillance based on primary tumour location.[1,2,13,14] A recent study conducted by Vernemmen et al. has demonstrated that the breast, lung and GIT are the primary origins of CMs. Intriguingly, for patients with GIT and lung cancer, particularly males, the head and scalp emerged as the most common sites for CMs. This is in stark contrast to cases of breast cancer in females, where the anterior chest wall was identified as the predominant location for CMs. This distinction underscores the significance of considering the primary cancer type and patient gender when assessing the prevalent sites for metastatic spread.[16] Most non-melanoma CMs were non-pigmented with prominent vascular structures, especially in lung and breast CMs. Among vessel types, linear serpentine vessels were most commonly detected across all types of CMs. Their prevalence could be attributed to angiogenesis.[11] Furthermore, our study unveils a recurring combination of dermatoscopic patterns—structureless white with linear serpentine vessels—in most non-pigmented CMs, regardless of their origin. This pattern could serve as a diagnostic clue and could help to distinguish CMs from other skin proliferations.

Our study comes with several limitations. First, its retrospective nature and the method of case selection are likely prone to selection bias. As a result, neither the frequency of primary tumours nor the anatomical locations of the CMs in our cohort may accurately reflect the broader landscape of CMs in cancer patients. Additionally, we did not perform a direct

comparison of the dermatoscopic features of CMs with a control group comprised of similar lesions with different diagnoses. It is also worth noting that isolated metastases are relatively uncommon; CMs are more often disseminated and can usually be diagnosed without the aid of dermatoscopy. Consequently, the practical utility of dermatoscopy in this context may be limited.

In conclusion, dermatoscopy serves as a valuable asset for the identification of solitary cutaneous metastases. Our study underscores the importance of conducting targeted dermatological examinations, particularly focusing on areas frequently affected by distant metastases like the head and neck region in cases of renal, breast, lung and GIT cancer, including the frontal thoracic wall especially in the case of breast cancer, as a standard component of oncological patient care.

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CONFLICT OF IN TER E ST STATEMEN T

The manuscript has been seen and approved by all authors, and their statements are listed below: Dr. Danica Tiodorovic, Dr. Jelena Stojkovic-Filipovic, Dr. Giuseppe Argenziano, Dr. Susana Puig, Dr. Linda Tongeti, Dr. Rubegni Pietro, Dr. Bengu Nisa Akay, Dr. Holger A. Haenssle, Dr. Christine Müller-Christmann, Dr. Elisa Cinotti, Dr. Jean Luc Perrot, Dr. Pedro Zaballos, Dr. Renato Marchiori Bakos, Dr. Aimilios Lallas, Dr. Zoe Apalla, Dr. Juergen F. Kreusch, Dr. Isabelle Tromme, Dr. Maria Antonietta Pizzichetta, Dr. Caterina Longo, Dr. Andreas Blum, Dr. Masuru Tanaka, Dr. Rainer Hofmann-Wellenhof, Dr. Andrija Jovic, Dr. John Paoli, Dr. Marija Buljan, Dr. Martina Espasandin-Arias, Dr. Horacio Cabo, Dr. Sonia Rodrigiez Saa, Dr. Gabriel Salerni, Dr. Gianluca Nazzaro, Dr. Grazyna Kaminska-Winciorek, Dr. Giovani Damiani and Dr. Franciska Geszti have nothing to disclose. Dr. Ashfaq Marghoob: FotoFinder, DermLite, Canfield (Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events), Heine (Receipt of equipment, materials, drugs, medical writing, gifts or other services); Dr. Josep Malvehy: Dermavision Solutions (Royalties or licences), ISDIN, Almirall, La Roche Posay, Pierre Fabre (Consulting fees), La Roche Posay, ISDIN (Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events), Almirall, La Roche Posay (Support for attending meetings and/or travel); Dr. Iris Zalaudek: Sanofi Genzyme, Sun Pharma, Novartis, MSD, BMS, Philogen, Biogena, La Roche Posay, Kyowa Kirin, FotoFinder, Mallinckrodt, Cieffe Derma, Pierre Fabre, Regeneron, Canova (Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events-made to author), Sunpharma (Support for attending meetings and/or travel to author); Sanofi Genzyme, Sunpharma, Philogen (Participation on a Data Safety Monitoring Board or Advisory Board to author); Board Member of the European Association of Dermato-Oncology, Treasurer of the Melanoma World Society, Past President of the International Dermoscopy Society (Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid). Dr. Luc Thomas: 3GEN, Jeine, Casio, FotoFinder (Receipt of equipment, materials, drugs, medical writing, gifts or other services Dermoscopy, Photo Dermoscopy and Digital Dermoscopy equipments to institution). Dr. Ketty Peris: Abbvie, Almirall, Lilly, Novartis, Sanofi, SIDeMaST (Grants or contracts from any entity (if not indicated in item #1 above to Institution)), Galderma, Leo Pharma, Lilly, Sanofi, Sun Pharma (Consulting fees to author), Sanofi, Sun Pharma (Support for attending meetings and/or travel), Abbvie, Almirall, Biogen, Galderma, Leo Pharma, Lilly, MSD, Pierre Fabre, Sun Pharma, Janssen, Sanofi (Participation on a Data Safety Monitoring Board or Advisory Board to author), Member of the Board Directors Catholic University, Rome, Italy (Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid). Dr. Alexander J. Stratigos: Abbvie, Lilly, LEO Pharma, Pfizer (Grants or contracts from any entity (if not indicated in item #1 above to Institution)), Sanofi (Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events to Institution); EADO Vice President, EADV Immediate Past President (Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid). Dr. Lidija Kandolf: MSD, Merck, ABBVIE, Janssen (Consulting fees), BMS, MSD, Novartis, Merck, ROCHE, ABBVIE, Janssen (Payment or honoraria from lectures, presentations, speakers bureaus, manuscript writing or educational events), BMS, MSD, Novartis, Janssen (Support for attending meetings and/or travel);Dr. Harald Kittler: Casia, Heine, Meta-Optima (Royalties or licences – to institution), FotoFinder, Novartis, Eli Lily, Pelpharma (Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events to author), AI Medical Technology, FotoFinder (Participation on a Data Safety Monitoring Board or Advisory Board), Heine, FotoFinder (Receipt of equipment, materials, drugs, medical writing, gifts or other services to author), International Dermoscopy Society (Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

APPENDIX

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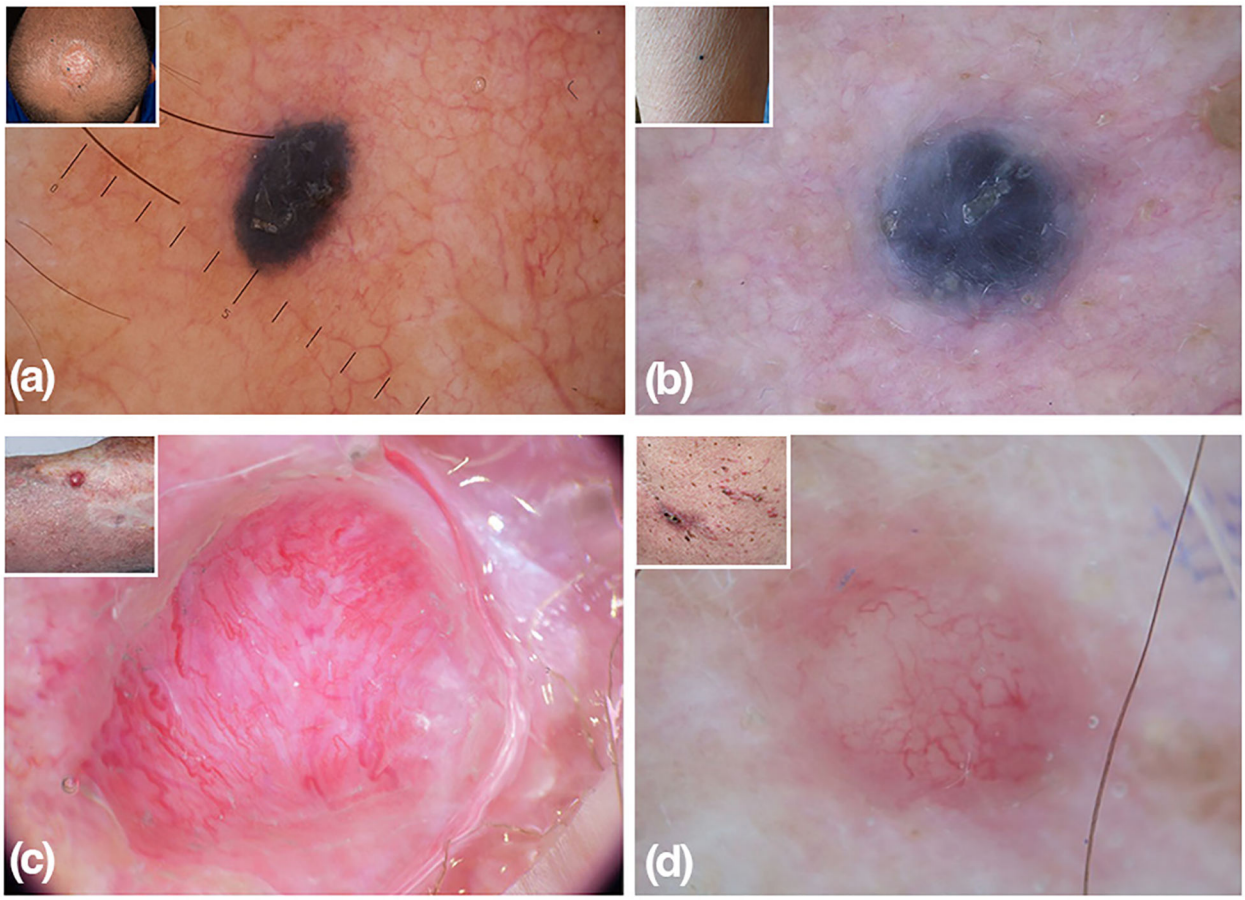

FIGURE 1.

Clinical and dermatoscopical presentations of melanoma CMs. (a, b) Pigmented melanoma CMs showing structureless blue pattern; (c, d) Non-pigmented melanoma CMs revealing structureless white pattern with linear serpentine vessels.

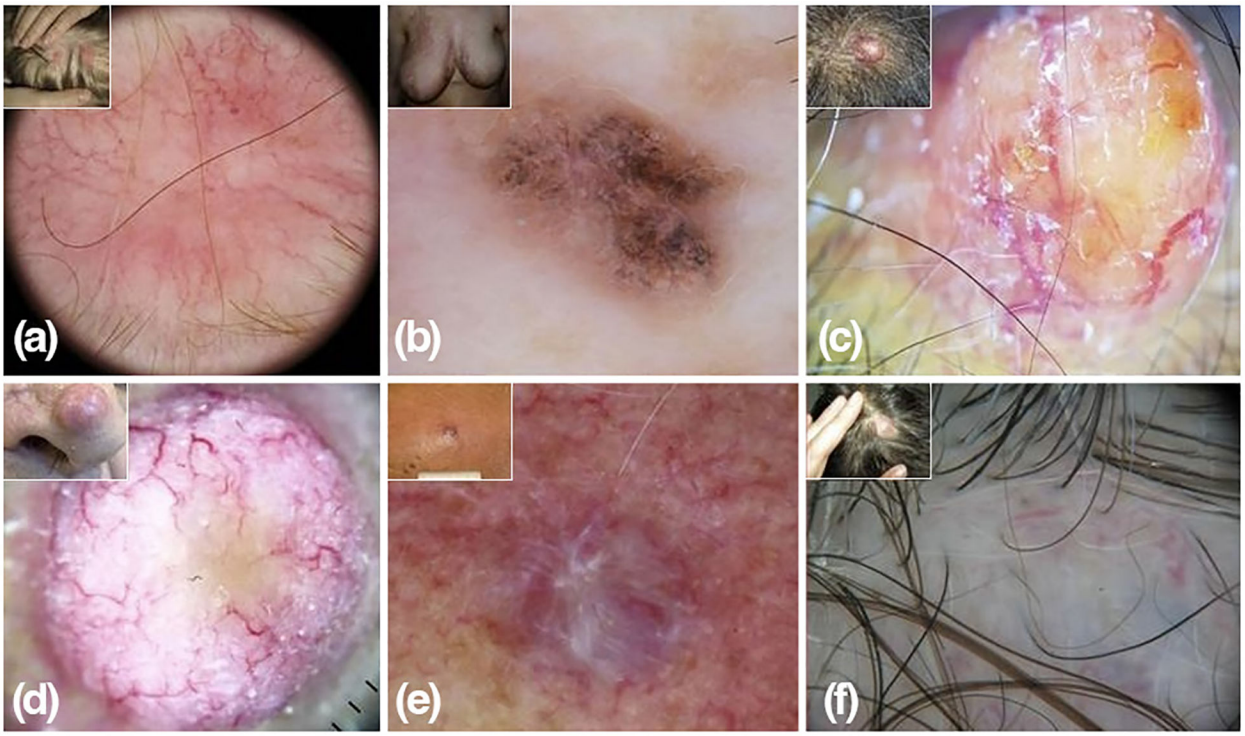

FIGURE 2.

Clinical and dermatoscopical presentations of non-melanoma CMs. (a) Non-pigmented breast CM showing structureless white pattern with linear serpentine vessels; (b) Pigmented breast CM showing clods and white lines on structureless brown pattern; (c) Non-pigmented CM of colon adenocarcinoma revelling structureless white pattern with linear serpentine vessels; (d) Non-pigmented CM of rectal adenocarcinoma revealing structureless white pattern with linear serpentine vessels; (e) Non-pigmented CM of renal carcinoma showing structureless white pattern with white lines and linear serpentine vessels; (f) Non-pigmented CM of lung cancer showing structureless white pattern with linear serpentine vessels.

TABLE 1

Frequency and categorization of primary tumours.

Cutaneous metastasis	***N* (%)**
Melanoma	**474 (75)**
Internal malignancies	**136 (21.51)**
Breast cancer CM	59 (9.34)
Lung cancer CM	21 (3.32)
GIT CM	25 (3.96)
Renal CM	12 (1.89)
Other	19 (3.01)
Merkel cell carcinoma CM	6 (0.95)
Ovarian cancer CM	4 (0.63)
Thyroid carcinoma CM	2 (0.32)
Squamous-cell carcinoma (non-skin) CM	4 (0.63)
Parotid glands carcinoma CM	1 (0.15)
Salivary ductal carcinoma CM	1 (0.15)
Cholangiocarcinoma CM	1 (0.15)
Non-melanoma skin cancer	**22 (3.48)**
Basocellular carcinoma	2 (0.32)
Squamous-cell carcinoma	20 (3.16)
Total*N*(%)	**632 (100)**

Abbreviations: CM, cutaneous metastases; GIT, gastrointestinal tract cancer.

TABLE 2

Frequency of distant CMs of different primary tumours.

	Metastases locations *N* (%)							
Primary neoplasm	**Genital**	**H&N**	**LE**	**Trunk**	**UE**	**Multiple**	**Missing**	**Total (*N*)**
Breast	0 (0)	15 (42.9)	0 (0)	18 (51.4)	2 (5.7)	0 (0)	0 (0)	35
GIT	1 (4.0)	8 (32.0)	1 (4)	11 (44)	0 (0)	3 (12)	1 (4)	25
Lung	0 (0)	7 (33.3)	1 (4.8)	12 (57.1)	0 (0)	1 (4.8)	0 (0)	21
Melanoma	0 (0)	10 (17.5)	16 (28.1)	11 (19.3)	7 (12.3)	11 (19.3)	2 (3.5)	57
NMSC	0 (0)	3 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3
Other	1 (6.2)	6 (37.5)	1 (0)	8 (50)	0 (0)	0 (0)	0 (0)	16
Renal	0 (0)	5 (41.7)	0 (0)	5 (41.7)	2 (16.7)	0 (0)	0 (0)	12
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Total *N*(%)	2 (1.2)	54 (32.0)	19 (11.2)	65 (38.5)	11 (6.5)	15 (8.9)	3 (1.8)	169

Abbreviations: GIT, gastrointestinal cancer; H&N, head and neck; LE, lower extremities; NMSC, non-melanoma skin cancer; UE, upper extremities.

TABLE 3

Frequency of structureless white pattern plus serpentine vessels in non-pigmented CMs of different primary malignancy.

	Structureless white pattern plus serpentine vessels		
Primary neoplasm	**Absent *n* (%)**	**Present *n* (%)**	**Total *N* (%)**
Breast	5 (9.3)	49 (90.7)	54
GIT	7 (28)	18 (72)	25
Lung	3 (14.3)	18 (85.7)	21
Melanoma	54 (34.2)	104 (65.8)	158
NMSC	2 (9.5)	19 (90.5)	21
Other	1 (5.6)	17 (94.4)	18
Renal	2 (16.7)	10 (83.3)	12
Total *N* (%)	74 (23.9)	235 (76.1)	309[a]
Melanoma	54 (34.2)	104 (65.8)	158
Non-melanoma	20 (13.2)	131 (86.8)	151
Total *N* (%)	74 (23.9)	235 (76.1)	309[b]

[a] $\chi^2 = 22.868 \cdot df = 6 \cdot$ *Cramer's V* $= 0.272 \cdot$ *Fisher's p* $= 0.001$.

[b] $\chi^2 = 17.443 \cdot df = 1 \cdot \varphi = 0.245 \cdot p = 0.000$.